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ERNEST A. SPIEGEL: COMMEMORATING HIS 65TH BIRTHDAY

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Ernest A. Spiegel was born in Vienna in 1895. The son of a physician, he entered the University of Vienna and received his M.D. degree in 1918. While a student he had begun to work at the Neurological Institute under Obersteiner and, later, Marburg, and became an assistant in the year of his graduation. Between 1918 and 1930 Doctor Spiegel pursued anatomical and physiological studies at the Neurological Institute, and at the same time was engaged in clinical work with Karplus at the Policlinic. At the early age of 29 he received the "venia legendi," thus joining the faculty of his alma mater. In 1930, when Doctor D. J. McCarthy instituted a research foundation at the reorganized Medical School of Temple University, Doctor Spiegel was invited to head the Department of Experimental Neurology and to become Professor of Experimental and Applied Neurology. This invitation was based in part upon the recommendation of Doctor J. C. Yaskin, one of Doctor Spiegel's many American postgraduate students. Despite numerous and attractive offers from other institutions, Doctor Spiegel has remained at Temple University for the last 30 years.

Limitations of space do not allow the complete enumeration of his publications (over 340); it must suffice to mention some highlights. Doctor Spiegel has published five monographs: *Muscle Tone* (8) in 1927; *Centers of the Autonomic Nervous System* (9) in 1928; *Experimental Neurology* (10) in 1928; *Neurology of the Eye and Ear*, with J. Sommer (German Edition in 1931, 11), (Spanish Edition in 1937), (English Edition in 1944, 31); and *Stereoencephalotomy* (36) in 1952 (with H. T. Wycis). He has also held the editorship of Confinia Neurologica and of Progress in Neurology and Psychiatry.

While studying the comparative anatomy of the forebrain ganglia, Doctor Spiegel discovered in 1918 a cell group on the undersurface of the psalterium and fornix respectively, which he designated as the ganglion psalterii (12); it was subsequently described by Putnam (6) as the intercolumnar tubercle and by Pines (5) as the subfornical organ.

In contrast to the concept prevailing at that time, that the central nervous system is only secondarily affected in generalized anaphylactic shock, Spiegel was able to demonstrate local cerebral reactions in this condition (28); at a later period the existence of localized allergic reactions of the central nervous system became generally accepted. By injecting small, intravenously ineffective extracts of various endocrines into the third ventricle of rabbits, an action upon hypothalamic vasomotor centers, particularly a depressor effect of pituitary extracts, was demonstrated in 1924 (30). The same effect was later described by Cushing (2) in man.

A series of systematic studies dealt with the influence of the labyrinth upon the vegetative nervous system, particularly the vascular system. A fall of blood pressure (23, 24) and an impairment of the cerebral circulation (25) was demonstrated and analyzed, a finding that was later confirmed by numerous investigators. Of his numerous

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studies on the physiology and pathology of the central connections of the labyrinth, the demonstrations of a cortical projection partly to the temporal and partly to the frontal lobe seem the most outstanding. A temporal connection was first established by the method of strychninization of circumscribed cortical areas (14, 15). When the temporal lobe of cats was sensitized to afferent impulses by localized application of strychnine, labyrinthine stimulation by rotation elicited epileptiform convulsions, apparently because the impulses entering the temporal cortex spread to motor areas. Further electrographic studies indicated that labyrinthine impulses partly entered the temporal lobe and partly the frontal lobe (16). The finding that the temporal lobe receives labyrinthine impulses seems to be applicable to man, since vertigo was observed in temporal lobe tumors more frequently than in other types of brain tumors (21). Penfield's (4) more recent observations of vertiginous seizures, elicited by stimulation of the temporal lobe on the operating table, are in full agreement with Spiegel's findings.

In recent years the reticular formation has become the happy hunting ground of physiologists, pharmacologists and clinicians. Strangely enough, it has been more or less ignored that as early as 1925, preceding Magoun's (3) work in this region by two decades, Spiegel showed that the rigidity of decerebrate cats is not completely abolished by lesions of the vestibular nuclei, but that the lesions had to encroach upon the reticular formation of the rhombencephalon in order to induce complete flaccidity. Historically-minded readers will find that as early as 1927 Spiegel had clearly outlined the importance of the reticular formation as a supraspinal reflex center of the static innervation in his monograph on muscle tone (8), as well as in Bethe's easily available *Handbuch der Physiologie* (13) two years later.

Regarding studies on the central part of the autonomic system, one can mention briefly and in passing Spiegel's experiments demonstrating that the pyramidal tract carries corticofugal fibers to the vegetative system (27).

Basic electroencephalographic studies were begun by Spiegel in Rothberger's Vienna laboratory, shortly before his departure to this country. Continuing these studies in Philadelphia, he was able to show, in 1936, that the electrocorticogram and the electrothalamogram may be widely independent of each other, that rhythmic discharges may be lead off from the thalamus of cats after decortication, and conversely, that rhythmic discharges can be obtained from the sigmoid gyri after interruption of their connections with the rest of the brain (17). Similar findings were made independently by Bremer (1) somewhat later on the occipital cortex.

An essential part of his professional contribution is the result of the joint efforts of Doctor Spiegel and his wife, the physicochemist Mona Spiegel-Adolf, who herself is widely known for her monographs on *Globulins* (49) and on *X-Ray Diffraction Studies in Biology* (50) as well as for her studies on the reversibility of protein coagulation, on the effects of irradiation on proteins, on the physicochemistry of lipids, and her spectrographic studies on the cerebrospinal fluid. In their joint work, the Spiegels were able to show that electric measurements of the polarizability of the cerebrum can be used as an index of permeability of semipermeable cell membranes, and that epileptogenic agents (32, 33) as well as cerebral concussion (26) increase the cellular permeability in the cerebrum. In concussion, it was further demonstrated that nucleases appear in the cerebrospinal fluid (34), and electrographic studies revealed that subcortical areas are particularly affected (35). The present writer was privileged to collaborate in some of these joint studies.

Historically it is interesting that Spiegel's

development of a method for quantitative study of the convulsive reactivity by electric stimulation of experimental animals with the skull intact (19), preceded the development of electroshock treatment of psychotic patients, an application that was suggested to him, but seemed to him inadvisable because of possible undesirable complications. This basic work served as an investigative tool for present-day anticonvulsant drug therapy in epilepsy.

In the winter of 1946, when prefrontal lobotomies were at the height of their popularity, Spiegel proposed to the writer that this operation be replaced by circumscribed lesions of the dorsomedial nucleus of the thalamus, the cell group that is the nodal point of the thalamo-frontal circuits. By limiting the lesions to this system and avoiding injury of cerebral association and commissural systems, it was hoped to avoid the personality changes appearing after the lobotomies.

This idea was the starting point of a new branch of neurosurgery, the stereotaxic surgery or stereoencephalotomy. Execution of this plan necessitated not only the construction of a human stereotaxic apparatus (stereoencephalotome) for introduction of guided electrodes, but also the development of a new type of cerebral topic anatomy determining the coordinates of subcortical structures in relation to intracerebral reference points.

In 1947 the first human stereoencephalotome could be described and the first thalamotomies (37–39) were reported; the first stereotaxic atlas of the human brain (36) and the results of variability studies were published within a few years. Further applications of stereoencephalotomy, treatment of so-called intractable pain by stereotaxic interruption of the spinothalamic system in the midbrain (40), of extrapyramidal disorders by pallidoansotomy (Huntington's chorea, 41, Parkinsonism, 43, 44, 53), of certain types of convulsive disorders (45) and of cystic tumors by injection of radioisotopes (52), soon became a reality. Besides its practical aspects, the possibility of introducing guided electrodes into the human brain with minimal cortical injury (46, 48, 51) has also greatly increased the scope of research by means of depth electrography and stimulation. As pointed out by Riechert (7) at the First International Neurosurgical Congress, stereotaxic surgery, since its introduction in 1947, has experienced an unexpected and strong development. This has been evidenced by the construction of about two dozen modifications of stereotaxic devices by various authors in this country and abroad, by symposia (Montevideo, 1955, Brussels 1957, Detroit 1957) and by the publication of three more stereotaxic atlases of the human brain.

The writer was indeed fortunate to have the opportunity to work in Doctor Spiegel's laboratory as a medical student. The association and attachment to this great scientist increased over time, and it was eventually possible, with him, to apply experimental neurophysiological investigations to clinical neurosurgical and neurophysiological problems in the human. Once Spiegel remarked, "Manus manum lavat" (he is fond of expressing his pleasures or displeasures in pointed Latin phrases), and this is especially true in the development of stereotaxic surgery. He has an uncanny gift for improvisation in the face of an obstacle or difficult situation, and on numerous occasions this faculty has been of great help, particularly during operative procedures.

Besides being a man of professional stature he is a kind, considerate and gentle physician, doing to others what he would have them do for him and not expecting from others what he himself could not do. His characteristically untiring energy and effort, however, make it difficult for others to keep pace with him.

Beside him always stands his gracious, loyal wife, a scientist in her own right. Unfailingly she has been our third hand and

during our daily noon discussions her opinions are sought on a host of problems.

On his sixty-fifth birthday Doctor Spiegel can look back on a professional career filled with notable achievements. His indefatigable spirit spurs him to further work, and his many colleagues and friends wish him continued success with his numerous ongoing projects.

REFERENCES

1. Bremer, F. Effets de la déafférentation complète d'une région de l'écorce cérébrale sur son activité électrique spontanée. Compt. rend. Soc. de biol., **127:** 355–358, 1938.
2. Cushing, H. Application of drugs to ventricles of the brain. Proc. Nat. Acad. Sc., **17:** 163–170, 1931.
3. Magoun, H. W. and Rhines, R. *Spasticity: The Stretch-Reflex and Extrapyramidal Systems.* Thomas, Springfield, Ill., 1948.
4. Penfield, W. and Jasper, H. *Epilepsy and the Functional Anatomy of the Human Brain.* Little, Brown, Boston, 1954.
5. Pines, J. L. Über ein bisher unbeachtetes Gebilde im Gehirn einiger Säugetiere; das subfornikale Organ des III. Ventrikels. J. f. Psychol. u. Neurol., **34:** 186–193, 1926.
6. Putnam, T. J. The intercolumnar tubercle. Bull. Johns Hopkins Hosp., **33:** 181–182, 1922.
7. Riechert, T. Die stereotaktischen Hirnoperationen. In *Ier Cong. Internat. Neurochirurgie,* pp. 121–160. Acta Medica Belgica, Brussels, 1957.
8. Spiegel, E. *Der Tonus der Skelettmuskulatur.* Springer, Berlin, 1927.
9. Spiegel, E. *Die Zentren des autonomen Nervensystems.* Springer, Berlin, 1928.
10. Spiegel, E. A. *Experimentelle Neurologie.* S. Karger, Berlin, 1928.
11. Spiegel, E. A. and Sommer, J. *Oto-Opthalmo-Neurologie.* Springer, Berlin, 1931.
12. Spiegel, E. A. Das Ganglion psalterii. Anat. Anz., **51:** 454–462, 1918.
13. Spiegel, E. A. Tonus. In *Handbuch der normalen und pathologischen Physiologie,* Bethe, A., ed., Vol. 9, pp. 711–740. Springer, Berlin, 1929.
14. Spiegel, E. A. The cortical center of the labyrinth. J. Nerv. & Ment. Dis., **74:** 504–512, 1932.
15. Spiegel, E. A. Rindenerregung durch Labyrinthreizung. Ztschr. f. d. ges. Neurol. u. Psychiat., **138:** 178–193, 1932.
16. Spiegel, E. A. Labyrinth and cortex. Arch. Neurol. & Psychiat., **31:** 469–482, 1934.
17. Spiegel, E. A. The electrothalamogram. Tr. Am. Neurol. A., 1936, p. 53.
18. Spiegel, E. A. Comparative study of the thalamic, cerebral and cerebellar potentials. Am. J. Physiol., **118:** 569–579, 1937.
19. Spiegel, E. A. Quantitative determination of the convulsive reactivity by electric stimulation of the brain with the skull intact. J. Lab. & Clin. Med., **22:** 1274–1275, 1937.
20. Spiegel, E. A. Effect of labyrinthine reflexes on the vegetative nervous system. Arch. Otolaryng., **44:** 61–72, 1946.
21. Spiegel, E. A. and Alexander, A. Vertigo in brain tumors, with special reference to the results of labyrinth examination. Ann. Oto. Rhin. & Laryng., **45:** 979–987, 1936.
22. Spiegel, E. A. and Bernis, W. J. Die Zentren der statischen Innervation und ihre Beeinflussung durch Klein-und Grosshirn. Arbeiten Neurol. Inst., Wiener Univ., **27:** 197–224, 1925.
23. Spiegel, E. A. and Demetriades, T. Einfluss des Vestibularapparates auf d. Gefässystem. Arch. ges. Physiol., **196:** 185–199, 1922.
24. Spiegel, E. A. and Demetriades, T. Der zentrale Mechanismus der vestibulären Blutdrucksenkung und ihre Bedeutung für die Entstehung des Labyrinthschwindels. Arch. ges. Physiol., **205:** 328–337, 1924.
25. Spiegel, E. A., Henny, G. C. and Wycis, H. T. Changes of cerebral circulation induced by labyrinthine stimulation. Am. J. Physiol., **142:** 589–593, 1944.
26. Spiegel, E. A., Henny, G. C., Wycis, H. T. and Spiegel-Adolf, M. Effect of concussion upon the polarizability of the brain. Am. J. Physiol., **146:** 12–20, 1946.
27. Spiegel, E. A. and Hunsicker, W., Jr. The conduction of cortical impulses to the autonomic system. J. Nerv. & Ment. Dis., **83:** 252–274, 1936.
28. Spiegel, E. A. and Kubo, K. Anaphylaxie und Nervensystem. Ztschr. ges. exper. Med., **38:** 458–477, 1923.
29. Spiegel, E. A. and Price, J. B. Vestibulocerebral pathways. Arch. Otolaryng., **26:** 658–667, 1937.
30. Spiegel, E. A. and Saito, S. Ueber die hormonale Erregbarkeit vegetativer Zentren. Arbeiten Neurol. Inst., Wiener Univ., **25:** 246–260, 1924.
31. Spiegel, E. A. and Sommer, I. *Neurology of the Eye, Ear, Nose and Throat.* Grune & Stratton, New York, 1944.
32. Spiegel, E. A. and Spiegel-Adolf, M. Fundamental effects of epileptogenous agents upon the central nervous system. Am. J. Psychiat., **92:** 1145–1168, 1936.
33. Spiegel, E. A. and Spiegel-Adolf, M. Physicochemical mechanisms in convulsive reactivity. J. Nerv. & Ment. Dis., **90:** 188–209, 1939.
34. Spiegel, E. A., Spiegel-Adolf, M. and Wycis, H. T. Cerebral concussion. Histochemical demonstration of nucleases in the cerebrospinal fluid. Arch. Pathol., **42:** 175–181, 1946.
35. Spiegel, E. A., Spiegel-Adolf, M., Wycis, H. T., Marks, M. and Lee, A. J. Subcortical changes in cerebral concussion. J. Neuropath. & Exper. Neurol., **7:** 162–171, 1948.

36. Spiegel, E. A. and Wycis, H. T. *Stereoencephalotomy* I. Grune & Stratton, New York, 1952.
37. Spiegel, E. A., Wycis, H. T., Marks, M. and Lee, A. J. Stereotaxic apparatus for operations on the human brain. Science, **106:** 349–350, 1947.
38. Spiegel, E. A. and Wycis, H. T. Physiological and psychological results of thalamotomy. Proc. Roy. Soc. Med. (supp.) **42:** 84–93, 1949.
39. Spiegel, E. A., Wycis, H. T., Freed, H. and Orchinik, C. The central mechanism of emotions. (Experiences with circumscribed thalamic lesions) Am. J. Psychiat., **108:** 426–431, 1951.
40. Spiegel, E. A. and Wycis, H. T. Mesencephalotomy in treatment of "intractable" facial pain. A.M.A. Arch. Neurol. & Psychiat., **69:** 1–13, 1953.
41. Spiegel, E. A. and Wycis, H. T. Pallido-thalamotomy in chorea. Arch. Neurol. & Psychiat., **64:** 295–296, 1950.
42. Spiegel, E. A. and Wycis, H. T. Role of pallidum in genesis of some choreic movements. Neurology, **3:** 261–266, 1953.
43. Spiegel, E. A. and Wycis, H. T. Ansotomy in paralysis agitans. A.M.A. Arch. Neurol. & Psychiat., **71:** 598–614, 1954.
44. Spiegel, E. A., Wycis, H. T. and Baird, H. W., III Long-range effects of electropallidoansotomy in extrapyramidal and convulsive disorders. Neurology, **8:** 734–740, 1958.
45. Spiegel, E. A., Wycis, H. T. and Baird, H. W., III Pallidotomy and pallidoamygdalotomy in certain types of convulsive disorders. A.M.A. Arch. Neurol. & Psychiat., **80:** 714–728, 1958.
46. Spiegel, E. A. and Wycis, H. T. Thalamic recordings in man with special reference to seizure discharges. Electroencephalog. & Clin. Neurophysiol., **2:** 23–27, 1950.
47. Spiegel, E. A., Wycis, H. T. and Reyes, V. Diencephalic mechanisms in petit mal epilepsy. Electroencephalog. & Clin. Neurophysiol., **3:** 473–475, 1951.
48. Spiegel, E. A., Wycis, H. T., Baird, H. W., III and Szekely, E. G. Functional state of the basal ganglia in extrapyramidal and convulsive disorders. A.M.A. Arch. Neurol. & Psychiat., **75:** 167–174, 1956.
49. Spiegel-Adolf, M. *Globuline*. T. Steinkopff, Dresden, 1930.
50. Spiegel-Adolf, M. and Henny, G. *X-Ray Diffraction Studies in Biology and Medicine*. Grune & Stratton, New York, 1947.
51. Wycis, H. T., Lee, A. J. and Spiegel, E. A. Simultaneous records of thalamic and cortical (Scalp) potentials in schizophrenics and epileptics. Confinia neurol., **9:** 264–272, 1949.
52. Wycis, H. T., Robbins, R., Spiegel-Adolf, M., Meszaros, J. and Spiegel, E. A. Studies in stereoencephalotomy. III. Treatment of a cystic craniopharyngioma by injection of radioactive P^{32}. Confinia neurol., **14:** 193–202, 1954.
53. Wycis, H. T. and Spiegel, E. A. Ansotomy in paralysis agitans. Confinia neurol., **12:** 245–246, 1952.

PROGRESSIVE CEREBRAL DEGENERATION OF INFANCY

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In an effort to clarify further the group referred to as the "cerebral palsies," attention is directed to a small group of cases originally described as diffuse progressive degeneration of the gray matter of the cerebrum (1) or what has been more recently termed poliodystrophia cerebri progressiva (3). The cases which comprise this group have in common the fact that they involve exclusively the gray matter of the brain, in contrast to the leucodystrophies or the diffuse scleroses. There is no general agreement that the cases thus far reported consitute a nosological entity. For this reason a review of their clinical and pathological features seems desirable, in order to determine whether their separation into a distinct and separate group is justified.

There have been seven verified cases thus far reported. Still another cases, that of Jervis, probably falls into the category of the cases in question (6). This was a girl who died at five and one-half years of age with a picture of progressive mental deterioration leading to idiocy, and progressive motor impairment with increased muscle tone and generalized spasticity. There was no history of seizures or myoclonus. The pathological process was characterized by diffuse loss of ganglion cells in the entire cerebral cortex with overgrowth of neuroglia, atrophy of the cerebellum involving all cortical layers, and degeneration of the basal ganglia with accumulation of large amounts of lipid material consisting mainly of cholesterol.

The case of Jervis is similar to those reported by others, except for the lipid accumulation in the basal ganglia and the absence of seizures or myoclonus. The cell loss is similar to that seen in other reported cases and for this reason, together with the confinement of the process to the gray matter, it should be included in the group under consideration.

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CLINICAL FEATURES

Incidence: The condition is rare. Thus far only seven authentic and verified cases have been recorded (1, 3, 4, 5, 8). Jervis's probably also falls into this group (see Table 1).

Age: Except for the case of Freedom (5), which lived to an age of 19 years, all the recorded cases have concerned infants or children varying from three months to eight years of age. Girls have been affected in five instances and boys in two cases.

Familial incidence: In the few cases which have been recorded, familial incidence has usually not been found. In two of Ford's cases a brother and sister, aged seven and one-half and eight years respectively, were affected; and in Kramer's cases, two sisters were involved, aged four years and four months, and 8 years.

SYMPTOMS AND CLINICAL EVOLUTION

In all but one of the reported instances the disease has appeared in infancy, and death has occurred from three months to eight years of age. The exception was the case that lived to the age of nineteen, as noted above.

Birth history was normal in five instances and abnormal in the first two cases of Ford (4). In these instances the delivery was by version and extraction in one case (Case 1), and in the other labor was described as difficult, requiring artificial respiration for 30 minutes before the baby could breathe (see Table 2). For the most part the disorder has appeared after a normal birth. The development has been described as normal un-

til the occurrence of first symptoms (1). These have appeared after 7–8 months, when mental retardation was noted (3), and after four months (8) and six months (4). In other instances the development has been slow from the onset. In one such case walking and speech development were reported to be slow, and numerous abnormal eye movements were noted in the early days of life (5). In another, the infant was described as being always backward and slow, walking at two years and talking imperfectly at three years (4). In still another, the infant was seemingly unable to laugh, could not fixate objects, was unable to grasp, and had difficulty in holding up her head (8).

Convulsive seizures of various sorts have been a common feature of the history, and have appeared as a rule early in the disease. Grand mal seizures were described in four instances (1, 4, 5). One of the patients was reported to have fits of the salaam type (7). Seizures have appeared at six months (4), three years (5) and six years (4). In one case (1) the age of onset of the seizures was not known. Head dropping seizures (4) and focal motor seizures appeared in two cases.

Myoclonus has been an almost constant feature, and has been described or witnessed in six of the seven cases. This has appeared early at four months (7) and six months (4), or has been delayed in appearance until six years (4) (see Table 3).

Following a delayed onset of symptoms or onset from birth, and the appearance of seizures at some time during the course of the disease, the history in all instances is that of failure of proper development. In all cases reported there has been a history of

TABLE 1

Age, Sex and Family Incidence

Author	Age	Sex	Family Incidence
Alpers	3 mos.	F	None
For *et al.* (Case 3)	1–3	F	None
Christensen and Krabbe	2–6	M	None
Kramer	4–4	F	Sister afflicted
Jervis	5–5	F	None
Ford *et al.* (Case 1)	7–6	F	Brother afflicted
Ford *et al.* (Case 2)	8	M	Brother of above
Freedom	19	F	None

TABLE 2

Birth and Onset

Authors	Birth	Onset	
		At Birth	Delayed
Alpers	Normal	+	
Freedom	Normal	+	
Christensen and Krabbe	Normal		+ (7–8 mos.)
Ford *et al.* (Case 3)	Normal		+ (6 mos.)
Kramer	Normal		+ (4 mos.)
Ford *et al.* (Case 1)	Version and extraction	+	
Ford *et al.* (Case 2)	Difficult: artificial respiration, 30 mins.	+	
Jervis	Normal		+ (15 mos.)

TABLE 3

Mental Deficiency and Seizures

Author	Mental Deficiency	Seizures			
		Grand Mal	Myoclonus	Focal	Head nodding
Alpers	+	+	+		
Freedom	+	+			
Christensen and Krabbe	+		+		
Ford *et al.* (Case 1)	+	+	+		+
Ford *et al.* (Case 2)	+		+	+	+
Ford *et al.* (Case 3)	+	+	+	+	
Kramer	+		+		
Jervis	+	−	−	−	−

mental deficiency of varying degree. In five instances there has been a severe degree of mental deficiency (3, 4, 5, 8) and in the other two instances the presumption can be made from the clinical descriptions that the deficiency was also profound. In another case (6) progressive mental deterioration leading to idiocy was present.

Neurological features present some similarity. Despite varying degrees of involvement of various parts of the nervous system, all the recorded cases are to considerable degree alike, though not all have presented the same signs. Deafness and blindness were found in two instances (4, 8), and in one of these cases was associated with normal fundi (4); this condition was not noted in the other case. In two instances optic atrophy was present (1, 3). In one cases associated with optic atrophy the pupils failed to react to light; no pupillary abnormalities were recorded in the other reported cases.

Motor disturbances were present in all seven cases, but were not all of the same nature. In two instances spasticity of all the limbs was recorded (3, 5); in one case right hemiparesis (4); in another increased reflexes and right Babinski sign (4); in two instances muscular rigidity was recorded (1, 4); and in one other case hypotonia with increased reflexes and left Babinski sign was described (8). In another case generalized spasticity was present (6).

Ataxia was described in four instances (3, 4, 5). Choreoathetosis was described in two cases (4) and athetoid finger movements were observed in one case (5).

SUMMARY OF CLINICAL FEATURES

The clinical syndrome of progressive cerebral degeneration concerns infants and children. It has been recorded twice in families. It may be evident in faulty development from birth, or indications of it may be delayed from several months to two or three years. Failure of development is noted in walking and talking, as well as in motor development, and in all instances mental deficiency of a severe degree is noticed either from the beginning, or appears in mild degree and becomes steadily progressive to the time of death. Myoclonic twitchings are common, and grand mal seizures, head dropping episodes, and even focal motor seizures develop.

Examination reveals mental deficiency, sometimes blindness and deafness, the former with or without optic atrophy. Spasticity of all the limbs may be present, or there may be fractional features of pyramidal tract disease. Ataxia is sometimes seen.

The disorder is progressive. The mental deficiency becomes increasingly profound, the convulsive seizures persist and may terminate in status epilepticus, and the motor disturbances become more disabling.

PATHOLOGICAL FEATURES

The condition under consideration was described in 1931 by the writer as diffuse progressive degeneration of the gray matter of the cerebrum (1). It is characterized by diffuse areas of necrosis involving the gray matter of the cerebral cortex and the basal ganglia; in particular the frontal, parietal and occipital cortex, and the caudate, putamen, pallidum, thalamus and pons. The areas of necrosis are confined to the gray matter and sharply demarcated from the white matter. The underlying process is a marked loss of ganglion cells, with neuroglial hyperplasia, mild microglial response, very mild fibroblastic proliferation and rare gitter cells. The affected areas showed demyelination of the cortex and basal ganglia, with good retention of the myelin in the white matter.

In 1927 a similar case had been reported by Freedom (5), revealing a degenerative process involving the entire cerebral cortex, but more marked in the post-central gyrus, the insula, the occipital and temporal lobes, and in the hypothalamus, thalamus and striatum. Histologically, the cortical fibers were practically lost, and a similar severe loss was found in the hypothalamus, thala-

mus, pallidum and striatum. Microglial proliferation was pronounced in the cortex, at times with gitter cell formation and there was also proliferation of the astroglia. Laminar degeneration of the third cortical layer was seen everywhere and at times status spongiosus of the entire width of the cortex. The basal ganglia were affected similarly to the cortex.

In the case reported by Christensen and Krabbe (3) the cerebral cortex was atrophic. There was severe disruption of the laminar arrangement of the cortex, only the cortex of the insula escaping. The entire cerebral cortex was effected, except for the Cornu Ammonis, which was normal. The astrocytes were proliferated, and there was moderate proliferation of the microglia, where the tissue was soft. The basal ganglia and white matter were normal.

The patients recorded by Ford (4) are of great interest, because Cases 1 and 2 of his series involved a brother and sister. In Case 1 microscopic examination revealed extensive degeneration of the cerebral cortex, most severe in the deeper layers, leading in some areas to spongy softening. The process was severe in the left hemisphere and mild in the right. The astrocytes were hypertrophied and microglia cells laden with lipoid droplets were seen. Capillary proliferation was seen in some areas. There was a moderate loss of myelin in the underlying white matter. The basal ganglia were also affected. The thalamus, corpus subthalamicum and substantia nigra were affected on both sides. The striatum was affected on the left side only. The cerebellar cortex and dentate nuclei were degenerated, and many Purkinje cells were lost. No inclusion bodies were seen.

In Ford's Case 2, the process was of the same type as Case 1, but it was less extensive and less destructive.

In Ford's Case 3 the process was much more severe in the right cerebral hemisphere. Here there was an "extraordinary loss of neurons in the cortex," most destructive in the 3rd and 4th layers, "where nothing was left except for a spongy reticulum of glial tissue which was traversed in places by bundles of fibers which were relatively well preserved." Moderate numbers of microglial cells laden with lipoids were seen. The process in the right cerebral hemisphere was of a similar nature but was less severe. The white matter and basal ganglia showed no definite changes. There was well marked degeneration of the cortex of the cerebellum, with destruction of many Purkinje cells and almost complete loss of the superficial molecular layer. There were no changes in the optic nerves or retinae.

The case reported by Kramer (8) involved the entire cerebral cortex, but was more severe in the temporal lobes, particularly the hippocampus. There were no changes in the white matter. The cortical changes were largely laminar, involving chiefly layers II and IV, which showed almost a complete loss of cells. Many of the remaining cells appeared undifferentiated and immature, especially in layers II and IV of the rhinencephalic portion of the temporal lobe. In some areas of the cortex there was spongy alteration of the ground substance. No fat was found. The axis cylinders were intact but there was a poverty of nerve fibers. Apart from a poverty of cells in the thalamus, diencephalon and mesencephalon, the basal ganglia showed no changes, but the findings were sufficiently prominent so that Kramer states, "Because of the lack of gray matter in the basal ganglia, strips of myelinate fibres predominated, giving the appearance of a status marmoratus." The cerebellum revealed cortical atrophy, and there was a loss of cells in all three layers in most lobules. The process was very marked in the hemispheres. Both dentate nuclei showed a poverty of cells and the left was underdeveloped. The nuclei of the pons were affected, only those of the facial nerve being practically normal. The nuclei of the medulla showed a

loss of cells which was pronounced in the olive, arcuate and hypoglossal nuclei.

In the case of Jervis (6) there was diffuse ganglion cell loss throughout the cerebral cortex with overgrowth of neuroglia, atrophy of the cerebellum involving all the cortical layers, and degeneration of the basal ganglia with accumulation of large amounts of lipid material consisting mainly of cholesterol.

All sections of the cerebral cortex showed severe changes and the normal architecture was no longer seen. The cells which remained were shrunken. Astrocytic neuroglia was increased and hypertrophied. The white matter showed no changes. Lipid material was found in abundance in the basal ganglia, throughout the caudate and pallidum. It was confined to the gray portion of the basal ganglia.

Localization of the process: In all the reported cases the disease has affected the gray matter, with complete sparing of the white substance except for minor changes. The cortex of the cerebral hemispheres has been affected in all cases. This is the most constant feature of the disease. In a few instances one hemisphere has been more affected than the other. For the most part the process has been equally severe in the affected hemisphere, but it has been found in greater intensity in the frontal, parietal and occipital areas, and again in the temporal areas, especially in the hippocampus. The basal ganglia have been involved often, but not invariably. In two instances (Ford, Case 3; Christensen & Krabbe) there was no involvement of the basal ganglia, and in a third (Kramer) the changes could be regarded as being unimportant. In another instance (Jervis) the basal ganglia were degenerated. In the cases in which the basal ganglia have been affected there has been no uniformity in the selection of the affected areas. The striatum and thalamus have been more frequently involved than other parts, and the thalamus has been often affected. The cerebellum was affected in four instances, leaving three of the reported cases in which nothing was found. There is little evidence on which to base impressions regarding localization. Changes in the pons and medulla, though recorded in some instances, appear to have no significance. The white matter was found to show evidence of demyelination in some instances, secondary to the changes in the cortex, but the process described in the cortex has never been seen in the white matter of brain or brainstem.

Histological features of the disease: The fundamental feature of the process is a loss of ganglion cells, invariably in the cerebral cortex, and in the basal ganglia and cerebellum when these are affected. The process is diffuse, but in some instances laminar degeneration is striking, with involvement of the deeper layers, the 3rd and 4th, and the 2nd and 5th layers. Proliferation of astrocytes occurs, and at times also of the microglia. Gitter cell formation is not striking, but microglia cells laden with lipoids have been recorded in some of the reported cases. Mild capillary proliferation is sometimes seen. The myelin structure of the affected gray matter of the cerebral cortex or basal ganglia is lost or decreased in content. When it affects the cerebellum, the process is much more pronounced in the Purkinje cell layer, but in some instances all layers of the cerebellum have been involved.

DISCUSSION

The problem posed by the cases under scrutiny is whether they constitute a nosological entity. This is bound up with the more general problem of poliodystrophies, and the question whether the evidence justifies the separation of a group of cases referred to as poliodystrophies in which there is selective involvement of the gray matter of the brain. Implication of the cerebral gray matter may occur in a number of conditions, but it is rare to find it involved without some simultaneous disease of the white substance. It has been objected that there

is no justification in establishing a morbid entity of poliodystrophy (2). There is available, however, evidence of selective disease of the gray matter in other disorders. Selective involvement of the gray matter of the spinal cord is found in progressive spinal muscular atrophy. It is also found in pure form in the brainstem in variants of amyotrophic lateral sclerosis. Cerebral forms of poliodystrophy are seen also in amaurotic family idiocy, gargoylism, and in Gaucher's disease. While these disorders have nothing in common with the present disorder, they at least indicate that selective involvement of the gray matter of the brain may occur.

The evidence for the grouping of the reported cases into a poliodystrophy group rests largely on the similarity of the histological findings. In all reported cases the disturbance has been limited to the gray matter, and the cerebral cortex and other affected parts of the brain have shown areas of cell loss, sometimes with status spongiosus, with mild reactive glial formation. The changes have been distinctive enough, though not the same in all instances, to fall into what appears to be a special group.

Though there is nothing which provides information regarding cause, there are a few bits of evidence which indicate that the condition is congenital. In two sets of cases, those of Ford, Livingston and Pryles (4) and those of Kramer (8), two members of the same family were afflicted. In Ford's cases the histological disturbance was the same in both cases. In Kramer's case the sister of the afflicted patient was reported to have multiple cystic softenings on gross examination of the brain. Subsequent examination (7) revealed that the case was one of multilocular encephalomalacia. Of even greater interest was the family history. In addition to the sisters, one with poliodysplasia cerebri and the other with multilocular encephalomalacia, two uncles of the father suffered from spinocerebellar degeneration and four cousins of the father had some spinocerebellar disease.

In some of the reported cases there has been evidence of immaturity in the development of the cortex, supporting the possibility that the process may have been congenital in origin. In these cases ganglion cells were seen in the white matter, and there were also numerous subependymal foci of immature cells. Not all the cases revealed findings of this nature.

Both the selectivity of the gray matter of the brain and the nature of the histological changes in the nervous tissue are similar to the changes observed in incomplete necrosis, or what has been termed elective parenchymal necrosis (9). These have been described by many observers, and have been regarded as the result of impairment of circulation. The histological changes associated with parenchymal necrosis are similar to those described in the poliodystrophies under discussion. These changes consist of loss of the parenchymal elements and atrophy of tissue but without frank softening and cavity formation. The process is regarded as the result of anoxia, and is based on the concept that the principal elements composing brain tissue vary in their sensitivity to anoxia, the neurones being most vulnerable, the neuroglia and mesoglia intermediate, and the vascular structures most resistant. There is no convincing evidence that the poliodystrophies under consideration are the result of anoxia. No data are available that anoxia was a factor during the intrauterine state, and in only two instances could this be regarded as a possible factor during the act of birth.

There appears to be sufficient evidence available that the group of cases first described as diffuse progressive degeneration of the gray matter and referred to as poliodystrophy cerebri progressiva, or progressive cerebral degeneration of infancy, constitute a clinical and pathological entity. The evidence for this lies in the fact that the changes are selective and affect only

the gray matter, that there is a similarity in the clinical picture of the affected cases, and that in a few instances the disease appears to have developed in two members of a family, and in another instance was found in conjunction with other forms of neurological disease in a single family.

REFERENCES

1. Alpers, B. J. Diffuse progressive degeneration of the gray mattter of the cerebrum. Arch. Neurol. & Psychiat., **25:** 469–505, 1931.
2. Benda, C. E. *Developmental Disorders of Mentation and Cerebral Palsies.* Grune & Stratton, New York, 1952.
3. Christensen, E. and Krabbe, K. H. Poliodystrophia cerebri progressiva infantilis. Arch. Neurol. & Psychiat., **61:** 28–43, 1949.
4. Ford, F. F., Livingston, S. and Pryles, C. V. Familial degeneration of the cerebral gray matter in childhood. J. Pediatrics, **39:** 33–43, 1951.
5. Freedom, L. Ueber einen eigenartigen Krankheitsfall des jugendlichen Alters unter dem Symptomenbilde einer Littleschen Starre mit Athetose und Idiotie. Deutsche ztschr. f. Nervenh., **96:** 295–298, 1927.
6. Jervis, G. A. Degenerative encephalopathy of childhood. J. Neuropath. & Exper. Neurol., **16:** 308–320, 1957.
7. Kramer, W. Multiocular encephalomalacia. J. Neurol. Neurosurg. & Psychiat., **19:** 209, 1926.
8. Kramer, W. Poliodysplasia cerebri. Acta psychiat. et neurol., **28:** 413–427, 1953.
9. Scholz, W. Die nicht zur Erweichung führenden unvollständigen Gewebsnekrosen. In *Handbuch der speziellen pathologischen Anatomie und Histologie,* Lubarsch, O. and Henke, F., eds., Vol. 13, pt. 1, pp. 1284–1325. Springer, Berlin, 1957.

THE PASSIVE MUSCLE RELAXATION IN PARKINSONISM: MYOGRAPHIC STUDIES OF THE PATHOPHYSIOLOGY OF THE RIGOR

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INTRODUCTION

Since Parkinson described his motor syndrome, six generations of neurologists have attempted to clarify this disturbance from a differential diagnostic and symptomatologic point of view and to differentiate it from other disturbances of motility, particularly from spasticity and catatonia. In the study of this motor disturbance, it became increasingly important to perfect myographic methods. Following the work of Rieger, these techniques have been developed by Spiegel, Filimonow, MacKinley and Berkowitz, v. Weiszäcker, Schaltenbrand and many others. It became clear that the rigor is not due to a locking of the skeletal muscles, as believed by Otfried Foerster, but that what is involved is a disturbance of innervation that is to be considered as a partial syndrome of decerebrate rigidity (4, 19).

The studies of Schaltenbrand and Hufschmidt, using a new combined mechano- and electromyograph, have demonstrated that in rigor of parkinsonism stretch reflexes as well as shortening and lengthening reactions may act closely together, and that there are in this respect many similarities with spasticity. Although in clinical examination parkinsonism is easily distinguished from spastic paresis, it is often very difficult to differentiate them by myography. Peculiarities such as shifting of the muscle balance of the extremities to the extensor or flexor side, for instance in the Wernicke-Mann type, the unusual activity of Hoffmann's proprioceptive reflexes, the fast fatigability of the spasm in contrast to the rigor, the appearance of pyramidal signs only in spasticity are still important diagnostic differential signs. It seemed desirable to use modifications of the technique of examination for further differentiation.

The myographic study of the parkinsonian patient is the only possible way of clarifying the pathophysiology of this disturbance of motility, since animal experiments do not succeed in imitating the picture of this disease. Certain drugs, such as bulbocapnine, produce a similar syndrome; however, this acts upon all levels of the central nervous system, while the theory of the extrapyramidal disturbances of motility at present assumes localized lesions in the brain stem.

In the disturbance of tonicity of parkinsonian patients one is apparently dealing with a disorder of the peripheral regulatory circuits of motor innervation. The monosynaptic or proprioceptive reflex discovered by Hoffmann (8) apparently does not play the important role that we have to ascribe to the polysynaptic myotatic reflexes of Sherrington. Even a spasticity can develop without a demonstrable proprioceptive reflex; in such cases the polysynaptic facilitating influences originating in the muscle spindles maintain the whole "voluntary" innervation, as shown by Asai and Hufschmidt (1).

Since tremor and the proprioceptive reflexes do not show a definite relationship, Jung (13) and Hassler (7) assume that the tremor is of central origin and has nothing to do with proprioceptive impulses. However, in the tremor of parkinsonism the proprioceptive impulses are the guiding force. These are not the monosynaptic pro-

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prioceptive reflexes, but polysynaptic influences from the Golgi organs. Hufschmidt (10) found that the effect of these centrally inhibiting receptors is so increased in parkinsonism that the slightest muscle tension is followed by inhibition, and that this may be the cause of the rhythmic muscle activity. According to our assumption, the innervation of parkinsonian patients is under the pathologically increased influence of inhibitory tension receptors, the Golgi organs. If this view is correct—and it is supported by the following experiments—a sudden passive relaxation of the voluntary innervation will induce a certain increase of the voluntary muscle activity which is released from the peripheral inhibitory impulses.

METHOD

The subjects were requested to contract voluntarily the biceps of the arm or the rectus femoris muscle, so that the forearm or the shank were slightly elevated. From these voluntarily innervated muscles, action potentials were led off by means of bare needle electrodes by way of RC coupled amplifiers with differential input and eventually recorded on an ink writer system of the "Schwarzer" type. The passive relaxation of the innervated muscles was performed by the experimenter's hand so that the forearm or the shank was passively moved in the direction of the muscle traction. The shank or the forearm was connected by a string with a leaf spring upon which strain gauges were glued. These strain gauges are part of a bridge circuit; the other part of the bridge is built into a carrier frequency amplifier which acts upon the writing system by means of a DC transmission.

RESULTS

In thirty-one parkinsonian patients the passive relaxation of the voluntarily innervated flexor muscles of the arm and of the extensor muscles of the leg was performed. Without exception, the passive relaxation resulted in a definite increase of the muscle potentials, while in normal individuals (Figure 1) no change of the innervation pattern can be noted. The latency from the beginning of the passive relaxation to the appear-

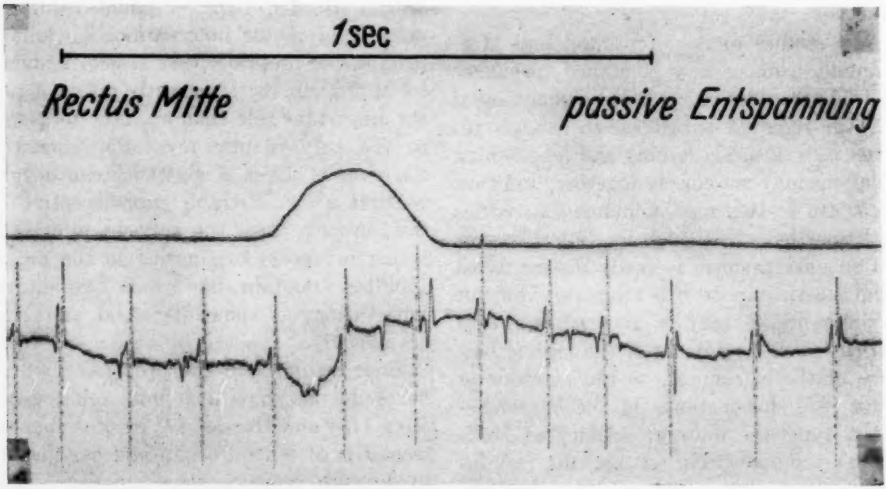

FIG. 1. Passive relaxation of muscles in a normal subject. Activity of a motor unit of the rectus femoris muscles. The curve above the muscular action potentials shows the mechanical course of the passive relaxation. In all curves the speed of recording is the same, *i.e.* 10 cm./sec. On passive relaxation the frequency of the motor unit does not change.

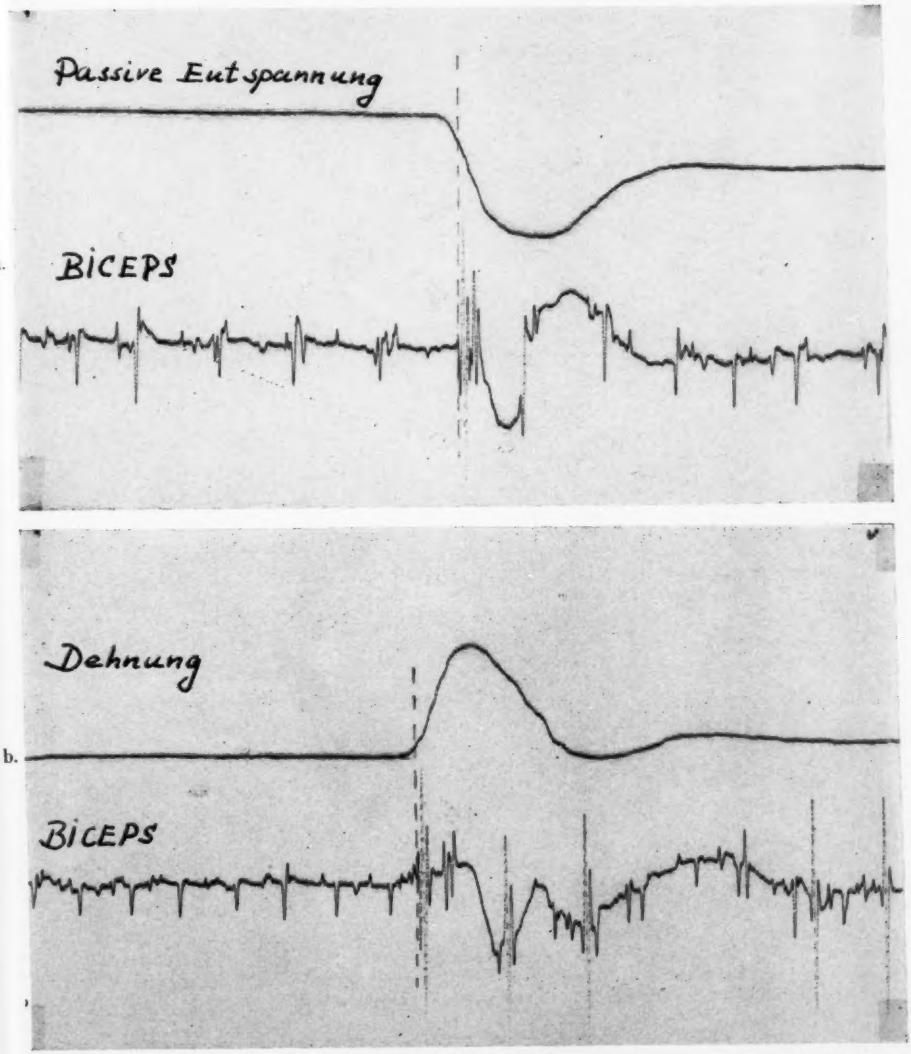

FIG. 2. a) Passive relaxation of the voluntarily innervated flexor muscles in a parkinsonian patient. The slightly rhythmic impulses are followed by a sudden discharge that appears 20–30 msec. after the beginning of the mechanical change. b) Distension of the biceps in the same person; about 20 msec. after the beginning of the stretching, there appears a definite stretch reflex.

ance of the increased innervation is in most cases very short; for instance, it is between 20 and 30 msec. (Figure 2a) for the biceps. In the thigh muscles the latency is usually somewhat longer. Figure 2b shows the effect of a distension of the biceps in the same subject. Surprisingly, the picture is the same. Apparently in parkinsonism the muscle spindles activated by way of the gamma system are also hypersensitive so that

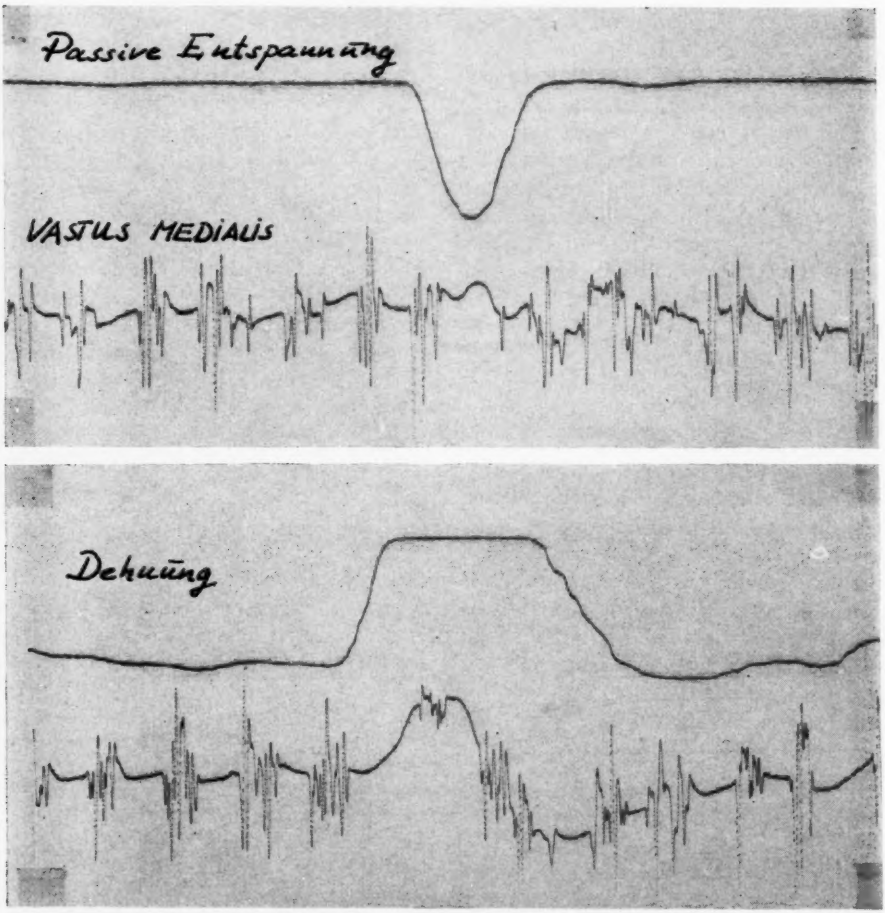

FIG. 3. a) Passive relaxation of the voluntarily innervated quadriceps muscle in a parkinsonian patient. The action potentials show a definite rhythm that hardly appears on mechanical recording. The intervals of the tremor become shorter due to the premature discharges. b) On stretching of the same muscle the tremor beat is suppressed.

promptly a pathologic stretch reflex results (see the following discussion). In the passive relaxation, however, the absence of the inhibitory impulses from the Golgi organs is responsible for the increase of the innervation.

Occasionally, however, one finds that stretching may have the opposite effect, namely an inhibition of the innervation, as shown by a comparison of Figures 3a and 3b. Here the general inhibitory influence from the Golgi organs dominates the gamma system. In a relatively small number of parkinsonian patients (six among 31) we found particularly long latency periods following passive relaxation until the beginning of increased activity.

Occasionally there may be a short preceding inhibition (Figure 4), as known from cases of spasticity.

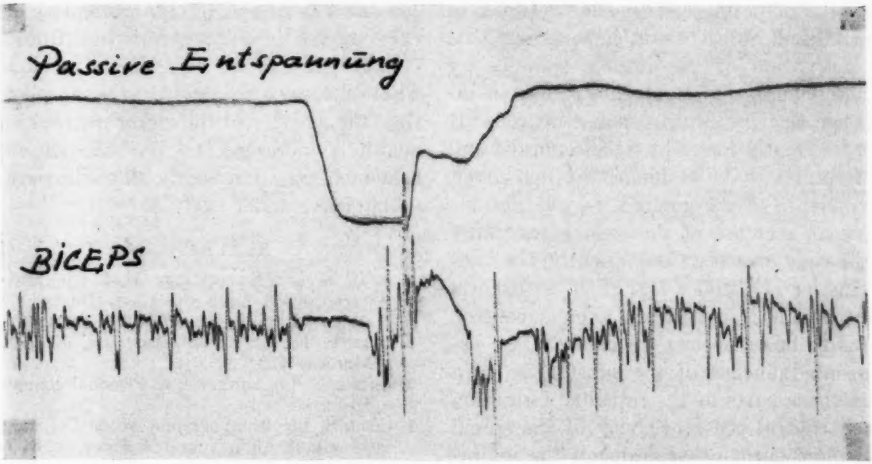

FIG. 4. On passive relaxation, the voluntarily innervated biceps of a parkinsonian patient first shows a short inhibition of 100 msec. This is followed by a significant increase of innervation with tendency to formation of rhythm.

DISCUSSION

In normal individuals it is found that stretching as well as a passive relaxation of the voluntarily contracted musculature, if not excessive, does not produce changes of the muscle potentials. In stretching the length as well as the tension receptors are equally stimulated. In passive relaxation the discharges from the tension and from the length receptors decrease at the same rate. It was concluded (11) that the impulses from the length receptors centrally integrate with those from the tension receptors in such a way that, if they are balanced, the central impulses to the motor neurons by way of the pyramidal tract determine the degree of contraction of the muscles without being influenced. In pathologic cases, for instance in spasticity, the sensitivity of the length receptors is changed by means of the gamma system so that the central integration results in favor of the facilitating impulses from the muscle spindles. Apparently this is a compensation of the interrupted central impulses to the motor neurons. Thus in spasticity, on slight distension we find the pathologic stretch reflex, and on passive relaxation, it becomes obvious that the activity of the motor neurons is driven only by the facilitating impulses of the muscle spindles. As a result the so-called "voluntary" innervation is absent (1). In a preceding paper (10) it was shown that in Parkinson's disease the inhibitory influence from the tension receptors is greatly increased. Since the Golgi organs, in contrast to the muscle spindles, do not have a central innervation and their sensitivity can not be centrally regulated, it was assumed that the sensitivity of the interneurons which transmit the inhibitory impulses may be changed by the central nervous system (23). Thus we assume a continuous dampening of the Parkinson innervation by inhibitory impulses from the Golgi organs; if the muscle tension decreases, as in passive relaxation, the activity of the anterior horn cells must increase considerably, as shown by our experiments.

Another point which must be discussed is the increased gamma activity in parkinsonism. The pathologic stretch reflexes appearing in parkinsonism (19) point in this di-

rection. Furthermore, Brune and Schenck, in unpublished observations, have shown that on activation of the muscle spindles by succinylcholin, the rigid part shows an increased activity of the motor neurons. It was frequently found by Schaltenbrand and Hufschmidt that the Jendrassik maneuver, *i.e.* increase of the gamma innervation, induces an increase of the stretch resistance of the rigid muscles. Consequently, the view of Hassler (7), that a loss of the substantia nigra equals a loss of the gamma control, seems to be erroneous. In contrast, we assume an influence of the substantia nigra upon those parts of the reticular formation which control the sensitivity of the spinal cord interneurons that transmit the inhibitory impulses from the Golgi organs. Animal experiments in this direction are in progress in our department.

A few cases show on passive relaxation an initial cessation of innervation as it is known in the spastic syndrome. Further studies will have to ascertain whether this is a special type of parkinsonism. Clinically these cases showed no sign of spasticity. In some of these patients, shortly after this cessation of innervation, an increase of innervation was recorded. Apparently an additional release must have taken place. The fact that this increase appears later than the cessation of innervation depends on the different time parameters of the length and tension receptors. The first act according to the differential quotient, the latter linearly (15).

SUMMARY

On passive relaxation of voluntarily contracted muscles, the facilitating impulses from the muscle spindles and the inhibitory impulses from the Golgi organs are absent for a short time. In normal individuals this does not induce significant changes of the activity of the motor neurons, apparently because facilitating and inhibitory impulses balance each other in the central nervous system. However, in parkinsonism the motor neurons are under the increased influence of the inhibitory impulses from the Golgi organs, as has been shown previously. Thus on sudden reduction of the muscle tension, the activity of the motor neurons must definitely increase. This phenomenon could be demonstrated in nearly all of the parkinsonian cases under study.

REFERENCES

1. Asai, K. and Hufschmidt, H.-J. Die Entlastungsreaktion beim Spastiker. Deutsche Ztschr. f. Nervenheilk., **178**: 289–299, 1958.
2. Bremer, F. *Le tonus musculaire*. Bergmann, Munich, 1932.
3. Brune, F. and Schenck, E. Personal communication.
4. Cobb, S. Electromyographic studies of paralysis agitans. Arch. Neurol. & Psychiat., **8**: 247–264, 1922.
5. Cobb, S. Muscle tonus (a critical review based on work presented at the International Neurological Congress, Bern, 1931) Arch. Neurol. & Psychiat., **28**: 661–678, 1932.
6. Dodt, E. and Gohl, D. Ein Fall fehlender Sehnenreflexe bei einem gesunden Menschen und seine neurophysiologischen Untersuchung. Deutsche Ztschr. f. Nervenheilk., **168**: 30–34, 1952.
7. Hassler, R. Die extrapyramidalen Rindensysteme und die zentrale Regelung der Motorik. Deutsche Ztschr. f. Nervenheilk., **175**: 233–258, 1958.
8. Hoffman, P. *Untersuchungen über die Eigenreflexe (Sehnenreflexe) menschlicher Muskeln*. Springer, Berlin, 1922.
9. Hufschmidt, H.-J. Spielen die Eigenreflexe bei raschen Willkürkontraktionen eine entscheidende Rolle? Experientia, **12**: 36–37, 1956.
10. Hufschmidt, H.-J. Über die reflektorische Grundlage des Parkinson-tremors. Deutsche Ztschr. f. Nervenheilk., **179**: 298–308, 1959.
11. Hufschmidt, H.-J. Bausteine motorischer Regelung. Schweiz. Arch. Neurol. u. Psychiat., 1960. In press.
12. Hufschmidt, H.-J. and Schaltenbrand, G. Elektromyographische Analyse der sogenannten Areflexien. Deutsche Ztschr. f. Nervenheilk., **179**: 252–266, 1959.
13. Jung, R. Physiologische Untersuchungen über den Parkinsontremor und andere Zitterformen beim Menschen. Ztschr. f. d. ges. Neurol. u. Psychiat., **173**: 263–332, 1941.
14. Lloyd, D. P. C. Conduction and synaptic transmission of reflex response to stretch in spinal cats. J. Neurophysiol., **6**: 317–326, 1943.
15. Matthews, B. H. C. Nerve endings in mammalian muscle. J. Physiol., **78**: 1–53, 1933.
16. Renshaw, B. Activity in the simplest spinal reflex pathways. J. Neurophysiol., **3**: 373–387, 1940.

17. SCHALTENBRAND, G. Verhalten der myotatischen Reflexe bei verschiedenen Tonusstörungen. Deutsche Ztschr. f. Nervenheilk., **136**: 2–14, 1935.
18. SCHALTENBRAND, G. Myographie. Naturforschung and Medizin in Deutschland. Dieterichsche Verlagsbuchhandlung, Wiesbaden, 1939–1946.
19. SCHALTENBRAND, G. AND HUFSCHMIDT, H.-J. Myographische Analyse des Parkinsonsyndroms. I. Congrès Int. Sc. Neurol., 1957.
20. SCHALTENBRAND, G. AND HUFSCHMIDT, H.-J. Die Rolle des extrapyramidalen Systems in der menschlichen Motorik. In *Einführung in die stereotaktische Operation*. Thieme, Stuttgart, 1959.
21. SPIEGEL, E. A. Zur Methodik der Tonusuntersuchung am Menschen. Ztschr. f. d. ges. Neurol. u. Psychiat., **122**: 475–487, 1929.
22. SPIEGEL, E. A. Tonus. In *Handbuch der normalen und pathologischen Physiologie*, Bethe, A., ed., Vol. 18, pp. 711–740. Springer, Berlin, 1932.
23. SUDA, I., KOIZUMI, K. AND BROOKS, C. M. Reticular formation influences on neurons of spinal reflex pathways. J. Neurophysiol., **21**: 113–123, 1958.
24. THIÉBAUT, F. Syndromes Parkinsoniens. Etudes cliniques et électromyographiques comparées. Travail de la Clinique Neurologique de la Faculté de Strasbourg. 1955.

COMMENTS ON THE PHYSIOLOGY AND PATHOLOGY OF EYE MOVEMENTS IN THE VERTICAL PLANE

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Although most motor functions are represented in both sides of the brain, each cerebral hemisphere influences movements predominately on the opposite side of the body. This is especially true for motor functions of the limbs. The contralateral influence is probably greatest in distal portions of the extremities, less in the proximal regions, and still less in movements of the face, neck and trunk. As for conjugate ocular deviations, "sidedness" is well represented. Deviations of the eyes on command to the left are effected chiefly by the right cerebral hemisphere, while those to the right are effected by the left side of the brain. What of all other ocular activities, such as convergent, oblique or vertical motions? It would seem that true upward or downward deviations should be equally influenced by both halves of the brain and that these conjugate vertical eye movements should be equally represented in each of the two hemispheres (2).

In this communication an analysis will be made of the known data on the physiology and pathology only of ocular motions in the vertical plane. The purpose is to ascertain the anatomic substrate and physiologic correlates which are involved in vertical eye movement. The study is based on observations made on eye movements in man and monkey. Horizontal eye deviations, ocular convergence, head motions, and other phenomena which are associated with ocular motion will not be analyzed in this article. In considering the neuropathologic basis of defects in conjugate eye movements, the symptoms should not be interpreted as due to a lesion in a particular area of the central nervous system. The location of the lesion must be viewed in relation to intact parts of the brain which participate in the mechanisms of eye movement. The dysfunction is not only due to the direct effects of the lesion but also to disordered activity of preserved structures. Thus, some reasons for lack of conjugate eye movement in a particular direction may be 1) deficiency of excitatory impulses, 2) active inhibition, 3) spasm or overaction of oculomotor activity in an opposite direction, or 4) influences from vestibular, visual or other sensory inputs. These are but few of many possible mechanisms which may explain faulty conjugate eye movements. The paralysis of gaze is not due to a lesion in a hypothetical center. It will be shown that induction or paralysis of vertical eye movement is due to involvement of both sides of the brain at various levels along the oculomotor pathway and not in a nucleus or a theoretical center.

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NORMAL SUBJECTS

The alert normal subject can, at will, move the eyes conjugately in all directions. The globes also move reflexely or in association with other motions. Thus on bilateral closure of the eyelids the globes roll upward. This is known as Bell's phenomenon. The phenomenon is best observed in patients with a peripheral facial or Bell's palsy. In these cases, even though there is paralysis of the eyelids on one side, the patient actually attempts to close both eyes. It is the bilateral lid closure which is accompanied by an upward rolling of the eyes. Unilateral closure of the lids fails to induce associated movement in either eye. It should be noted that the phenomenon of upward rolling of the eyes on bilateral eye closure is found

in more than 90 per cent of the studied normal subjects. In three per cent the associated ocular deviations are downward.

Another example in which vertical eye movements may be induced by bilateral influences or stimulations can be found on simultaneous caloric stimulations of both vestibular systems. Bilateral cold water irrigation of ear canals with the subject's head in the erect position induces tonic downward deviation of the eyes and upward nystagmus; warm water stimulation induces upward tonic deviation of the eyes and downward nystagmus. In summary it is apparent that bilateral innervation, whether it be eyelid closure, or caloric vestibular stimulations, induces ocular movements in the vertical plane.

ELECTRIC STIMULATION OF BRAIN

Electric stimulation of the surface of one cerebral hemisphere in unanesthetized man may or may not induce contralateral horizontal conjugate eye movement. Stimulations of the frontal lobe often results in contralateral deviations of the eyes (14). At times these deviations manifest an upward or downward component. Strictly upward or downward deviations are rare occurrences in unilateral frontal stimulations, but since unilateral stimulations rarely induce vertical eye movements it is possible that such movements might be obtained on bilateral simultaneous stimulation of the brain. There have been few if any reports of simultaneous electric stimulations of foci in both cerebral hemispheres in man. Such experiments might be of value.

IRRITATIVE LESIONS CAUSING SEIZURES AND SPASMS OF EYE MOVEMENTS IN THE VERTICAL PLANE

From observation made in seizure disorders, it has been found that ocular deviations in the vertical plane are common, particularly in an upward direction. In all of these instances there is clinical and electroencephalographic evidence of a bilateral cerebral discharge. These patients show bilateral motor or sensory dysfunctions and there is often impairment of consciousness. It should be noted that unilateral focal seizures rarely if ever are accompanied by ocular deviation in the vertical plane. The foregoing observations suggest that both cerebral hemispheres must be "activated" whenever eye movement occurs in the vertical plane.

Oculogyric spasms or crises are well known phenomena in diseases of the basal ganglia. The spasms may occur either in the horizontal or vertical plane. The most frequent type is in an upward direction, less in other directions. Whatever the mechanism for the upward oculogyric spasm may be, it has been found that the pathologic process in these cases is almost always bilateral. These patients also have other evidence of bilateral nervous system dysfunctions.

Lesions in the upper midbrain or pretectum may also cause spasmodic deviations in the vertical plane. But here too the pathologic process implicates structures across the median raphe. There is bilateral involvement. Unilateral lesions rarely if ever manifestly induce vertical eye movements.

In summary, it is apparent that irritative phenomena, such as ocular seizures or spasms of ocular movements in the vertical plane occur only in patients with bilateral lesions of the brain.

LESIONS OF THE BRAIN CAUSING IMPAIRMENT OF CONJUGATE GAZE IN THE VERTICAL PLANE

UNILATERAL CEREBRAL HEMISPHERE

Large lesions of one cerebral hemisphere may cause impairment of contralateral horizontal gaze in addition to a hemiplegia. In these cases the eyes are often deviated away from the side of the hemiplegia. Vertical eye movements on command are generally preserved in these patients. However, under

certain circumstances a defect in the vertical plane may be demonstrated. Thus on strong closure of the lids of both eyes instead of the usual upward rotation, the globes move to the side of hemiplegia, on opening the globes move back to the opposite side (5). Also during sleep, the eyes in these patients may be deviated to the side of the hemiplegia, rather than upward; on awakening they move horizontally back to the opposite side or away from the hemiplegia. Bilateral simultaneous caloric stimulation of the labyrinths induces an oblique instead of the expected upward or downward movement and nystagmus.

Thus in cases of unilateral cerebral lesion although there is impairment of contralateral horizontal gaze there are also defects in the vertical plane. The latter, however, are manifest only under conditions of bilateral innervations, such as closing of both eyes or bilateral caloric stimulation of vestibular systems.

LESIONS OF THE BASAL GANGLIA

In lesions of the basal ganglia, oculomotor deficits may be manifest in an inability to move the eyes in the horizontal as well as in the vertical planes on command. Oculocephalic reflexes are preserved. Again in these cases the lesions are bilateral. Strictly unilateral lesions, which do not implicate the midline, rarely if ever cause impairment of movement in the vertical plane. There is no doubt there may be instances in which unilateral lesion may cause oculgyric spasms in the vertical plane but such cases must be rare. Oculogyric crises occur most frequently in post encephalitic states, a condition which is known to implicate both sides of the brain.

LESIONS OF THE PRETECTUM

Diseases in the region of the posterior commissure, habenulae and immediately adjacent structures known as the pretectum, often cause paralysis of upward gaze. Despite the upward gaze palsy there is no ptosis. In fact, there may even be bilateral eyelid retraction so that the patient will have a staring expression. Lesions in this area may occasionally cause paralysis of downward gaze. As a rule if present the palsy of downward gaze is in conjunction with a defect in upward gaze, or it is part of impairment of conjugate eye movement in all directions. The most frequent types of lesions in this region of the brain are tumor of the pineal body, vascular disease and inflammatory processes which occur in encephalitis. In all of these cases the pathology is bilateral. Tumor of the pineal body always compresses both sides of the pretectum. Vascular lesions or inflammatory processes although asymmetrical often involve both sides of the median raphe of this region. Even unilateral lesions in this area must be close enough to the midline to affect the opposite side. Analysis of some of the recently reported cases of so called unilateral vascular encephalomalacia causing paralysis of upward gaze, revealed that there were areas of rarefaction on both sides ventral to the posterior commissure and both habenular regions even though it was more on one side (1). Perusal of the numerous case reports on paralysis of vertical gaze which are frequently found in the literature and the sporadic review on the subject disclosed that paralysis of upward gaze and in some instances subsequent weakness of downward gaze occurred only in cases of bilateral lesions. In some instances there was emphasis on unilaterality of the lesion (7) but on closer examination it is evident that the destructive process if not a functional disturbance extends across the mid-line. In Spiller's article on paralysis of upward gaze which he published in 1905, an analysis of the cases he reported and those he reviewed from the literature indicates that the lesions were almost always bilateral (23). Although he called attention to the fact that the superior colliculi need not be involved in paralysis of upward gaze, he seemed to ignore the common finding of bilaterality of the

lesion. This neglect may have been due to the median location of the lesion so that the bilaterality did not seem significant.

LESIONS OF THE BRAIN STEM

Diseases of the brain stem often cause ocular disorders in all planes. The disorders may be manifest as varying degrees of paralysis of gaze in horizontal, oblique, rotatory or vertical direction as well as in different types of nystagmus. The ocular disturbances which occur in the vertical plane are most frequently observed in patients with lesions of the upper brain stem between the pretectum and the level of the oculomotor trochlear nuclear masses. Lesions in this region are apt to be bilateral because they are so near the mid-line.

There may be paralysis of upward gaze particularly when there is involvement of the periaqueductal zones at the level of the nucleus of Darkschewitsch. When the oculomotor nuclei or their rootlets are involved paralysis of vertical movement is not uncommon. Such patients usually manifest bilateral ptosis. In regions caudal to the 3 and 4 cranial nerve nuclei, paralysis or weakness of upward gaze occurs, but again the lesions are bilateral.

An analysis of cases of lesions in the tegmentum of the pons described in the early literature, revealed that paralysis of upward gaze occurred only when the lesions were on both sides of the mid-line (23). Even in more caudal lesions, such as in the upper medulla, interference of vertical eye movements was observed when the lesion was bilateral. In a case of bilateral softening of the paramedian zone of the upper medulla due to vascular disease, nystagmus was found in the vertical as well as in the horizontal planes (12). Defects in the vertical plane may also be obtained in bilateral lesions of the median longitudinal fasciculus. Clinical and anatomic studies of patients who had lesions of the median longitudinal fasciculus at levels between the 4th and 6th nerve nuclei revealed that upward nystagmus occurs only when the lesions are bilateral (5). There is no apparent defect in vertical eye movement or nystagmus when the lesion is unilateral. From the foregoing studies in man it is evident that 1) defects in the vertical plane may be elicited in patients with unilateral brain lesions but only on bilateral "innervations" or stimulation, and 2) manifest defects of ocular movements in the vertical plane occur in bilateral lesions of the brain, particularly along the oculomotor pathway in the pretectum or brain stem.

OBSERVATIONS ON ANIMALS

RESULTS OBTAINED IN STIMULATION OF THE CEREBRUM AND BRAIN STEM

Cerebrum: Unilateral stimulation of any part of the cerebrum in the unanesthetized monkey caused deviation of the eyes to the opposite side. In stimulation of the occipital lobe one often observed contralateral horizontal as well as oblique and even true vertical eye movement. Stimulation of the occipital lobe above the plane of the calcarine fissure caused true downward or obliquely downward conjugate eye movement, while stimulation below the plane induced an upward component (27). Also of significance is that in the anesthetized preparation one frequently found eye centering (3, 10). Ocular deviations were not as common and occurred mostly in the contralateral direction. Deviations in the vertical direction were rarely obtained even in stimulations of the occipital lobe (10). In the alert or unanesthetized monkey unilateral stimulation of the brain usually produced contralateral eye deviation. In these animals stimulation of one occipital lobe or to some extent one frontal lobe evoked ocular movement with a vertical component much more frequently than in the anesthetized preparation.

Most of the reported experiments have dealt with unilateral stimulations. There have been sporadic investigations on the

effects of bilateral simultaneous cerebral stimulations. Mott and Schaefer observed that faradic stimulation of bilateral symmetrical points in the anesthetized monkey caused the eyes to assume a mid-position as if they were looking straight ahead (11). At times they observed slight convergence movements. From some bilateral symmetrical points electric stimulation yielded either simple upward or downward movement. These investigators stated however, that movement in the vertical plane was obtained from areas which on single stimulation yielded contralateral deviation with an oblique component. Although unilateral stimulation of the cerebrum causes a contralateral horizontal conjugate deviation of the eyes in most instances, it must be borne in mind that the horizontal motion is not due to isolated contractions of the external rectus of the abducting eye and of the medial rectus of the adducting eye. All the extrinsic muscles of both eyes are in a continuous state of activity either in tonic or relaxed phase. The ocular effect produced by the cerebral stimulation is part of a patterned movement of the eyes and head acting as a unit. Stimulation in the same man or animal with head restricted may cause changes in the degree of eye movement and even in direction. Moreover, after section of the internal and external recti of the eyes in the monkey, stimulation of one cerebral hemisphere results in vertical rather than in contralateral horizontal eye movements (15).

Spiegel found that unilateral cerebral stimulation may also result in vertical eye movement after bilateral lesions in the brain stem (19). Thus stimulation of one frontal lobe after destruction of both sets of vestibular nuclei resulted in vertical instead of horizontal eye movements. Spiegel also found that after destruction of both sets of semicircular canals there occurs a nystagmus in the vertical plane (21). Again it is evident that it is the bilaterality of stimulation or of lesion which induces or alters the function of eye movement in the vertical plane. There probably are other examples in which bilateral lesions in regions of the lower brain stem cause defects in vertical eye movements, as expected on cerebral stimulation.

Brain Stem: There have been numerous observations on the ocular effects induced by electric stimulation in a variety of animals by various investigators. We, in our laboratory, have worked with both anesthetized and alert monkeys. In the anesthetized monkey electric stimulation of foci in the paramedian regions of the tegmentum, above the level of the oculomotor nucleus, causes contralateral deviation of the eyes, while stimulation below the level of oculomotor nucleus causes ipsilateral deviation. Although conjugate horizontal deviations are best obtained on stimulations of the paramedian zone, they may also be obtained from more lateral regions of the brain stem in the alert animal. As for vertical eye movements, these were much less frequent. An analysis of the vertical eye movements elicited on unilateral stimulation of the paramedian zone within or near the mid-line yields but few true vertical responses in the anesthetized monkey. It was found that true upward movements occurred on unilateral stimulations in the more dorsal and rostral regions of the brain stem. Downward movements were also obtained but these were rare, occurring mostly in the ventral and caudal portions of the brain stem. It should be noted that the foci which yielded vertical eye movements were the same which on stimulation resulted in horizontal eye movements. There were no "centers" which yielded a particular ocular movement. Conjugate upward, downward, or oblique ocular movements could be obtained on unilateral stimulation of the vestibular nucleus. The movements in the vertical plane are but part of a variety of ocular motions elicited from the vestibular

stimulations, or from stimulation of foci along the oculomotor pathway from the brain to the level of the vestibular nuclei.

Szentagothai, working with anesthetized cats or dogs, found that unilateral stimulation of the interstitial nucleus of Cajal caused conjugate eye deviations in the vertical and at times in a rotatory direction (24). In more lateral regions at this level the ocular responses were contralateral and horizontal. Spiegel and Scala found that unilateral stimulation of the brain stem in the region of the periaqueductal central gray matter caused upward movements of the eyes from the more rostral and less frequently downward deviations from caudal regions (20).

In the unanesthetized or alert monkey both the horizontal and vertical components of eye movements can be obtained on unilateral stimulation of foci over a more extensive region of the brain stem, even in areas lateral to the paramedian zone (17). Again, of the two types of movement in the vertical plane, those in an upward direction are much more frequent than those with a downward component. It should be noted that a greater incidence of upward eye movement is also found during convulsive seizures in man, and in patients with oculogyric spasms due to disease of the basal ganglia. Moreover, in the paretic or paralytic disorders, weakness of upward gaze is quite frequent, and defects on downward gaze are rare.

There have been a few observations made in our laboratory on simultaneous stimulations of both sides of the brain stem. Such stimulations sometimes caused a vertical eye movement but at times stimulation of the same points caused no response. The behavioral and anatomic data are incomplete. These experiments are still in progress.

From the foregoing observations it may be predicted that vertical eye movement may be more easily elicited on bilateral rather than unilateral stimulations of the brain stem. It is also evident that there are no centers which when stimulated electrically yield a specific type of eye movements. All types of ocular movement may be obtained on unilateral stimulation of oculomotor pathway.

Cerebellum: Stimulations of the cerebellum may yield conjugate eye movements. Such movements have been obtained largely from the vermis. The movements are often contralateral and horizontal but occasionally ipsilateral. Unilateral stimulation may also cause oblique and occasionally true upward or downward movement. Bilateral simultaneous stimulations may cause upward or downward movements.

Semicircular Canals: Bilateral cold caloric stimulation of the vestibular system in the monkey with the head in the erect position causes tonic downward deviation of eyes and upward nystagmus. Bilateral warm caloric stimulations induce upward deviation of eyes and downward nystagmus.[2]

From observations made on effects of

[2] The fact that vertical ocular responses were obtained only on bilateral simultaneous caloric stimulations of vestibular systems suggests that this was a resultant interaction between the influences of the right and left sets of semicircular canals. Since cold stimulation of one ear stimulates all three semicircular canals the resultant contralateral nystagmus is probably due to the unopposed action of the lateral semicircular canal; the action of the anterior canal being neutralized by that of the posterior canal. This conclusion is based on studies made on electric stimulation of single nerves emanating from each semicircular canal in decerebrate cats. Fluur (9) found that 1) selective stimulation of the nerve emanating from the left lateral semicircular duct resulted in conjugate eye movement to the right, 2) stimulation of the nerves from the left or right anterior canal elicited upward movements of both eyes, and 3) stimulation of the nerves either from the left or right posterior canal induced a downward movement. Similar conclusions were obtained in an earlier study by Szentagothai (25). On bilateral caloric stimulation of the ears the horizontal influences produced by the lateral canals oppose eath other, there being no resultant horizontal effect. The resultant vertical effects indicate that in the erect animal the anterior canals are more sensitive to cold, while the posterior more to warm stimuli.

stimulation in animals it is interesting to note that the ocular responses which occur on bilateral innervation in the monkey are almost the same as in man. Thus, bilateral eyelid closure in the monkey is invariably associated with upward movement of both globes. This is manifest on spontaneous closure of the eyes, blinking, or reflex closure of the lids induced by corneal stimulations. Also, bilateral caloric stimulation of the semicircular canals evokes eye movement in the vertical plane. In general it is the bilateral innervation or stimulation which readily induces either upward or downward movements in the globes in monkey and, as indicated previously, in man.

DEFECTS IN VERTICAL EYE MOVEMENTS CAUSED BY LESIONS OF THE CEREBRUM AND BRAIN STEM

Cerebral Lesions: Hemispherectomy or removal of large masses of cerebral tissue in the monkey may produce transient paralysis of horizontal gaze to the contralateral side (13). There is some difficulty in the vertical plane with this type of lesion, but this defect is brought out best by bilateral vestibular stimulation. In monkeys with hemispherectomy simultaneous stimulation of both vestibular systems may result in ocular deviation and nystagmus in the oblique instead of expected vertical planes. The alteration of vestibulo-ocular response in the vertical plane is also found in small circumscribed lesions. Thus 3 mm. lesions in the field of Forel on one side caused impairment of contralateral horizontal eye movements and on bilateral simultaneous stimulation defects in vertical eye movements or nystagmus could be elicited (16). Bilateral frontal lobectomies cause no significant change in eye deviations. Bilateral occipital lobectomy also fails to produce defects in eye movements in any plane in the young monkey.

Lesions of the Brain Stem: From Spiegel's extensive researches which are largely referred to his book (22), it has been shown that lesions in the brain stem cause defects in eye movements in the cat. In more recent experiments in our laboratory, small (1–2 mm.) unilateral lesions situated near the mid-line at or above the level of the oculomotor nucleus are seen to cause paralysis of contralateral gaze in the monkey. when the unilateral lesion is at or below the level of the trochlear nucleus, the defect is ipsilateral (26). However, there is no manifest paralysis of upward or downward gaze in these cases of unilateral lesions. Defects in the vertical plane could be elicited in these monkeys but only with special tests. In general it has been found that bilateral cold or hot caloric stimulation in monkeys with single unilateral lesion of the upper or lower brain stem revealed defects in the vertical plane (16). In unilateral lesions of the superior brain stem above the level of the oculomotor nucleus and 4 mm. to the side of the mid-line, bilateral cold water irrigation of the ear canals elicited defects in tonic downward nystagmus, whereas with warm water there was impaired downward nystagmus. On bilateral cold or hot caloric stimulation with lesion in the paramedian zone below the level of the oculomotor nucleus at 1 mm. from the mid-line, the defect was apparent for movements with an upward component. There was defective upward nystagmus during bilateral cold stimulations, and poor tonic upward deviation during stimulations with warm water. Each of the aforementioned defects in the vertical plane was also found on vestibular turning tests which induce either upward or downward movements[3].

[3] The defects in the vertical component of the vestibulo-ocular responses in these experimental lesions of the brain stem are contrary to what one would have predicted from observations made after bilateral lesions of the pretectum such as in pinealomas in man or after experimental destruction of the central gray matter in the cat as reported by Spiegel and Scala (20). Thus, in our monkeys with small unilateral lesions of the Fields of Forel, bilateral caloric stimulation elicited impairment of the downward component while in man bilateral lesions at this level cause defect in

In summary, unilateral lesions of the brain stem produce 1) distinct defects in horizontal conjugate gaze as well as impairment of the horizontal component of the vestibulo-ocular response on unilateral caloric stimulation, 2) disturbances in vertical eye movements, but this is observed only on bilateral vestibular stimulation.

Bilateral lesions of the brain stem cause manifest defects in vertical eye movement. A conspicuous and enduring paralysis of upward gaze can be produced by a lesion in the pretectum and the region about the posterior commissure. These lesions in the monkey are bilateral. In man the lesion of the pretectum which causes paralysis of upward gaze is almost always bilateral. In Spiegel's and Scala's experimental lesions of the central gray matter the destruction although seemingly unilateral implicated both sides of the mid-line. In these cats there was paralysis of upward and downward gaze. More recent studies in our laboratory revealed that 1 or 2 mm. lesions situated 1 mm. to each side of the mid-line in the tegmentum of the pons, cause not only paralysis of movement in the horizontal plane to right and left but also in the vertical, so that there was paralysis on upward and downward gaze. In some monkeys, when there was recovery of function, there was nystagmus upward and downward and some with unilateral downward nystagmus. These studies are also incomplete. Although we have been searching thus far we have found no particular area which when destroyed would produce an isolated paralysis on downward gaze in the experimental monkey. Paralysis of upward and downward gaze may be produced by bilateral lesions of the paramedian zone. As stated, there may be transient paralysis of conjugate eye movements in all directions. During recovery from such bilateral lesions a paralysis of downward gaze may be the only residual deficit. At this time the animal gives the appearance as if there were an isolated type of defect in downward gaze, but actually there were defects in all directions.

In monkeys with unilateral lesions of the median longitudinal fasciculus there is a defect in eyes for horizontal movement but none for motions in the vertical plane. However, when the lesion extends across the midline to implicate both median longitudinal fasciculi there occurs nystgmus in both eyes on upward gaze, and bilateral partial lid droop (4, 18). These studies of bilateral lesions of the median longitudinal fasciculus are incomplete. It is possible that a mid-line lesion in the caudal portions of these bundles may result in nystagmus on downward gaze.

In summary, analysis of oculomotor dysfunction caused by disease in the brain stem discloses 1) that only bilateral lesions conspicuously impair eye movements in the vertical plane and 2) that unilateral brain stem lesions interfere with vertical eye movements as elicited on bilateral simultaneous vestibular stimulations.

Lesions of the Cerebellum: Lesions of the cerebellar hemispheres *per se* seldom if ever cause defects in eye movement. Destruction of the flocculo-nodular node on one side causes transient contralateral mild conjugate deviation of eyes to the side opposite the lesion. Destruction of both sides of the posterior vermis may cause transient defects in conjugate eye movements in the vertical plane (8).

Lesions of the Semicircular Canals: According to Spiegel bilateral lesions of the semicircular canals cause nystagmus in the vertical canal (21). Unilateral lesions produced no defect in vertical eye movement.

the upward component. Conversely, small unilateral lesions in the paramedian zone of the tegmentum of the pons in the monkey produced impairment of the upward component on bilateral vestibular stimulation; while in man there is indirect evidence that more caudal lesions induce defects in the downward plane. These differences might be due to location of the lesion in relation to distance from the mid-line, its proximity to the oculomotor nucleus at which level the oculomotor pathways cross, the mode of crossing and whether the lesion is on one or both sides of the mid-line.

This is but another example in which the factor of bilaterality elicits dysfunction in the vertical plane.

DISCUSSION

From the foregoing observations on man and experimental animal it is quite obvious that either the induction or interruption of eye movements in the vertical plane involves both sides of the brain. All binocular conjugate eye movements are influenced by both sides of the brain. There is no specific type of eye movement which is subserved by a particular pathway. Patterns of eye movement are determined by the needs of the organism, the chief being to maintain clear single image vision. This is accomplished through the integrative action of the nervous system. The efferent impulses for all types of eye movement are transmitted through channels, converging toward the brain stem. The anatomy of these fiber pathways is not well defined. Various studies failed to disclose a definite corticobulbar pathway (27). The pathway may consist of several neurones. There are connections between the cortex and the cells in the reticular formation of the brain stem. From there short fibers project through the paramedian zone and median longitudinal fasciculus to the cells in the ocular and vestibular nuclei.

Based on methods of stimulation and lesion it is hypothecated that there must be a crossing of these pathways at about the level of the oculomotor and trochlear nuclei. Throughout the hypothetical oculomotor pathway the predominant type of conjugate eye movement which can be elicited on electric stimulation, and impaired by lesions, is one with the horizontal component. The direction of the horizontal vector changes at the decussation of the oculomotor pathway; it is contralateral when the fibers are stimulated above and ipsilateral below the decussation. The anatomic substrate for horizontal eye movement is probably bilateral even though a lesion on one side may interfere with horizontal movements, contralateral if the lesion is above, and ipsilateral if below the decussation.

As for the vertical eye movements the transmission of impulses is by the same oculomotor pathways as those which mediate the horizontal components. The mediation of impulses for vertical movements occurs equally on both sides there being no dominance as to laterality. There is no unilateral lesion which will manifestly abolish vertical eye movement. Unilateral lesions will impair vertical eye movements but this defect becomes apparent only on bilateral simultaneous stimulations of vestibular systems or on bilateral ocular innervations such as occurs during eye closure. Bilateral innervations of eyes and bilateral vestibular stimulations will induce vertical eye movements. Bilateral lesions across the midline of the brain stem will interfere with vertical eye movements. Whether there is a decussation between the fibers which transmit up and down vectors as there is between right and left horizontal components of ocular movement is not as yet clear. Since there are many instances of isolated paralysis of upward and few of downward gaze, one might assume that some regions in the brain transmit impulses predominately for upward eye movements. There must be other regions which transmit downward components. Even though these fiber systems are not anatomically defined, those which participate in the acts of up and down ocular motions probably decussate at the same level as those which are involved in right and left conjugate movements.

Based on the foregoing clinical experimental data it is suggested that there is an oculomotor pathway on each side of the brain. Each of these pathways transmits impulses for binocular vertical and horizontal gaze as well as for acts of convergence. The right and left pathways decussate at about the level of the 3rd and 4th cranial nerve nuclei. Above the decussation

the structures which influence upward movement are situated more medially, while the downward more laterally. Intermingled are the horizontal or contralateral "vectors." Below the decussation the impulses for all types of eye movements are transmitted through a smaller and more compact area localized to the paramedian zone of the tegmentum of the brain stem ventral to the median longitudinal fasciculus. Here the upward vectors may be situated slightly lateral to the downward, whereas the ipsilateral horizontal component is the most conspicuous of the three. All three vectors (up, down, and horizontal) which are represented on each side of the brain from the cortex to the ocular nuclei are probably influenced by impulses which originate in the three semicircular canals and the vestibular nuclei. All three ocular vectors are also influenced by an overall eye centering system. This system maintains the position of the globes in relation to the posture of the head and body. In other words, any deviation of the eyes from the center, whether it be in the horizontal or vertical direction, is tonically influenced by the eye centering system so that the globes tend to assume a central position (3). Ocular deviation or centering is achieved by mechanisms which involve the brain at different levels. There are no "centers" for a particular eye movement. Clinically oculogyric spasms or paralyses in the vertical plane are due to implication of either both sides of the cerebrum, basal ganglia, pretectum, or more caudal structures in the paramedian zone of the tegmentum of the brain stem.

SUMMARY

Analyses of vertical eye movements involved in normal ocular deviations, in eyelid closure and in response to vestibular stimulations were made in normal man.

Studies of vertical eye movements were also made in patients with seizure disorders, electric stimulation of the brain, as well as in patients with diseases of the brain, basal ganglia brain stem and cerebellum.

The data obtained in man were compared with those obtained in experimental animals, particularly the monkey.

It is evident that 1) induction of vertical eye movement usually requires bilateral innervation and 2) impairment of vertical eye movement is caused by lesions on both sides of the midline.

Theoretical pathways transmitting impulses for all eye movements are discussed.

REFERENCES

1. Angelergues, R., de Ajuriaguerra, J. and Hécaen, H. Paralysie de la verticalité du regard d'origine vasculaire. Étude anatomo-clinique. Rev. neurol., **96**: 301–319, 1957.
2. Bender, M. B. Pathways mediating vertical eye movements. Tr. Am. Neurol. A., **84**: 159–161, 1959.
3. Bender, M. B. The eye centering system. A. M. A. Arch. Neurol. & Psychiat., **73**: 685–699, 1955.
4. Bender, M. B. and Weinstein, E. A. Effects of stimulation and lesion of the median and longitudinal fasciculus in the monkey. Arch. Neurol. & Psychiat., **52**: 106–113, 1944.
5. Christoff, N., Anderson, P., Nathanson, M. and Bender, M. B. Problems in anatomic analysis of lesions of the median longitudinal fasciculus. A.M.A. Arch. Neurol., **2**: 293–304, 1960.
6. Cogan, D. G. Neurologic significance of lateral conjugate deviation of the eyes on forced closure of the lids. Arch. Ophth., **39**: 37–42, 1948.
7. Dereux, J. *Paralysie Verticale du Regard (Syndrome de Parinaud) Contribution à l'Étude de la Localisation de la Lésion*, p. 96. Arnette, Paris, 1926.
8. Duke-Elder, W. S. Impairment of conjugate vertical movements may occur in bilateral cerebellar lesions. In *Text-book of Ophthalmology*, Vol. 4, p. 4165. Mosby, St. Louis, 1949.
9. Fluur, E. Influences of semicircular ducts on extraocular muscles. Acta oto-laryngologica, supp. 149, 1959.
10. Krieger, H. P., Wagman, I. H. and Bender, M. B. Changes in state of consciousness and patterns of eye movements. J. Neurophysiol., **21**: 224–230, 1958.
11. Mott, F. W. and Schaefer, E. A. On associated eye movements produced by cortical faradisation of the monkey's brain. Brain, **13**: 165–173, 1890.
12. O'Brien, F. H. and Bender, M. B. Localizing value of vertical nystagmus. Arch. Neurol. & Psychiat., **54**: 378–380, 1945.

13. Pasik, P., Pasik, T. and Bender, M. B. Effects of hemidecortication upon various types of induced nystagmus in the monkey. Abstracts of communications 21st Internat. Congr. Physiological Sc., p. 207. Buenos Aires, 1959.
14. Penfield, W. and Boldrey, E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain, **60**: 389–443, 1937.
15. Russell, J. S. R. An experimental investigation of eye movements. J. Physiol., **17**: 1–26, 1894.
16. Shanzer, S. and Bender, M. B. Oculomotor responses on vestibular stimulation of monkeys with lesions of the brain-stem. Brain, **82**: 669–682, 1959.
17. Shanzer, S., Papatheodorou, C. A., Wagman, I. H. and Bender, M. B. Oculomotor pathways in brain stem as outlined by electrical stimulation. Fed. Proc., **16**: 511, 1957.
18. Shanzer, S., Wagman, I. H. and Bender, M. B. Further observation on the median longitudinal fasciculus. Tr. Am. Neurol. A., **84**: 14–17, 1959.
19. Spiegel, E. A. Role of vestibular nucleii and cortical innervation of the eye muscles. Arch. Neurol. & Psychiat., **29**: 1084–1097, 1933.
20. Spiegel, E. A. and Scala, N. P. Ocular disturbances associated with experimental lesions of mesencephalic central gray matter with special reference to central vertical ocular movements. Arch. Ophth., **18**: 614–632, 1937.
21. Spiegel, E. A. and Scala, N. P. Vertical nystagmus produced by peripheral labyrinthine lesions. Arch. Otolaryng., **40**: 160–163, 1944
22. Spiegel, E. A. and Sommer, I. *Neurology of the Eye, Ear, Nose and Throat*, p. 667. Grune & Stratton, New York, 1944.
23. Spiller, W. G. The importance in clinical diagnosis of paralysis of associated movements of the eye balls especially of upward, and downward associated movements. J. Nerv. & Ment. Dis., **32**: 417–448; 497–530, 1905.
24. Szentagothai, J. Die zentrale Innervation der Augenbewegungen. Arch. f. Psychiat., **116**: 721, 1943.
25. Szentagothai, J. The Elementary vestibulo-ocular reflex arc. J. Neurophysiol., **13**: 395–407, 1950.
26. Teng, P., Shanzer, S. and Bender, M. B. Oculomotor pathways determined by electrolytic lesions in brain stem. Am. J. Physiol., **187**: 636, 1956.
27. Wagman, I. H., Krieger, H. P. and Bender, M. B. Eye movements elicited by surface and depth stimulations of the occipital lobe of Macaque Mulatta. J. Comp. Neurol., **109**: 169–193, 1958.
28. Walberg, F. Do the motor nuclei of the cranial nerves receive corticofugal fibers? An experimental study in the cat. Brain, **80**: 597–605, 1957.

THE AROUSAL OF THE BRAIN

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The nature and mechanism of the effect exerted upon the telencephalon by the arousal impulses originating in the reticular formation of the brain stem are far from being completely elucidated. In this respect one may say that the discovery of this influence created more problems than it resolved, which in itself is indicative of the importance of a discovery.

The terms of desynchronization and electrocortical activation are quite convenient for description, and can be used interchangeably. This seems to have tended to blunt the curiosity of investigators, which these paradoxic phenomena should have stimulated to higher degree.

One of the most unexpected of these phenomena is the reduction in amplitude which the elementary responses of the cortex show when the animal passes from a state of superficial sleep or somnolence to awakening or alertness. First observed for the potentials of the acoustic area that were evoked by a short sound stimulus, this reduction has further been found for the responses of the other receptor areas of the cortex to a stimulus applied to their peripheral receptors. The secondary potentials which followed the primary response in the specific projection area (18), as well as those that accompany them in the association areas (7), are particularly vulnerable to this paradoxic suppressor action.

The interpretation of the phenomenon originally proposed by this writer (2) attributed it to a process of "masking" by occlusive convergence of the specific and the reticular ascending impulses in the cortical neuronal networks. However, this was only a conjecture without supporting experimental evidence. The hypothesis of an active inhibition exercised by the arousal impulses either directly upon the cortex or upon the transmission of corticopetal impulses at a subcortical level (12) has also been developed, in analogy with the selective blocking of ascending impulses which characterizes sensory attention.

Recently the question became more sharply defined when, independently, Dumont and Dell (11) and Bremer and Stoupel (5, 6) applied the test stimuli provoking the cortical response, instead of to peripheral receptors, to the afferent fibers that originate in these receptors (optic nerve or chiasma), or to the thalamic nuclei that relay the sensory afferent impulses. In these experiments, performed on the non-anesthetized brain of the encéphale isolé preparation (cat), the depression of evoked potentials in the reticular arousal (Figure 1; A and B) was regularly replaced by its potentiation (C and D). It appeared also that the repetitive rapid stimulation of the nuclei belonging to the nonspecific thalamic system had the same facilitating effect as the stimulation of the mesencephalic tegmentum (Figure 1; E, F, D). In both cases the facilitating effect of punctate stimulation of these structures was diffuse; it affected all projection areas of the neocortical convexity—visual, auditory (H, I, J) somaesthetic, associative areas. The effectiveness of the dynamogenesis was revealed by the possibility of observing a considerable reinforcement of the evoked potential by application, at convenient intervals, of a very short conditioning faradization—for instance, a group of five shocks at a frequency of 500/sec. (K, L, M), or a single electric shock to the reticular mesencephalic structures or to the nonspecific thalamic structures (K, L, M).

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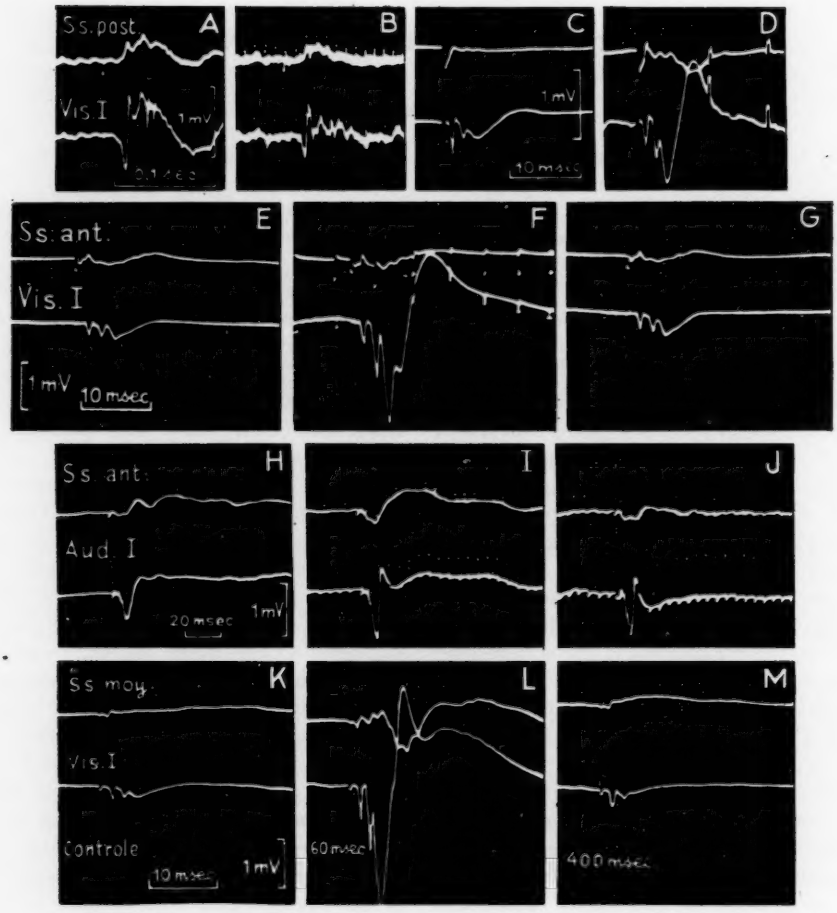

FIG. 1. Inhibition and facilitation of evoked cortical potentials in reticular arousal. Cats, encéphale isolé preparations; monopolar surface recordings, negatives upwards.

A and B: Responses of lateral (visual area) and suprasylvian gyri to a brief photic flash. C and D: Responses of the same cortical spots to a lateral geniculate shock; note the time scale difference—the B and D responses were obtained during the same stimulation of the mesencephalic RF (100/sec.; 0.3 msec.; IV). E and G: Control responses to a geniculate shock. F: Responses recorded during a brief repetitive stimulation of n. centromedianus. H: Responses of the middle ectosylvian (auditory) and suprasylvian gyrus to a medial geniculate shock. I and J: Responses recorded during a repetitive stimulation of the n. ventralis anterior at two different strengths. K: Responses of visual area and suprasylvian gyrus to a lateral geniculate shock. L and M: Responses to the same stimulus conditioned by a brief (10 msec. duration) stimulation of the mesencephalon at the indicated intervals—note in L the appearance of a response in the associative area.

The identification of the facilitating effect with an arousal phenomenon was justified by the possibility of observing it in sensory or amphetamine awakening (6) in identical form; furthermore, it coincided with the ocular and electrocorticographic signs of cerebral awakening and disappeared in barbiturate narcosis simultaneously with these symptoms.

These observations on evoked potentials

nay be related to experiments of Gellhorn *t al.* (13, 14), using pain and direct hypo-halamic stimuli in the intact animal and o the macro- and microphysiological ob-ervations of Jasper and Ajmone-Marsan (16), of Li (17), and Creutzfeld and Aki-moto (8), who studied the effect of con-vergence of thalamic nonspecific influences with specific afferent impulses in the visual and somaesthetic areas.

The interpretation of this facilitation of evoked cortical potentials in the reticulo-cerebral arousal does not seem to pose difficult problems. It has been shown (5) that this facilitation is located in the thalamic nuclei that relay the specific impulses, as well as in the cortex that is directly affected by the arousal impulses. This cortical factor certainly is the most important. All the peculiarities of the phenomenon relate it to the facilitations by heterosynaptic convergence of heterologous impulses. These faciliations are characterized by the possible contrast of the apparent insignificance of the response to the conditioning stimulus, if applied alone in relation to the effectiveness of its dynamogenic effect upon the response of a test stimulus (5, 15). One can also demonstrate an additive or substitutive interaction of the reticular facilitation with other cortical facilitating mechanisms (6).

It seems that all this takes place as if the physiologic mechanisms of cerebral arousal were using the general qualities of the neuronal heterosynaptic convergence, the mechanism of which probably consists of the subliminal depolarization of nerve cells that are the seat of the convergence created by the heterologous conditioning impulses.

The opposite effect of reticular arousal upon the evoked cortical potentials, if these are induced by stimuli applied to the peripheral receptors, is more difficult to interpret. One does not deal, at least as a principal factor, with an inhibitory blocking of sensory impulses in the relay nuclei of the afferent pathway, since it has been demonstrated by Desmedt and La Grutta (10) and our own confirmatory and additional observations that the response of the medial geniculate body to a click can not be modified in the moment where the response of the acoustic area is completely abolished, in the cerebral awakening produced by a sensory or a direct reticular stimulus.

The hypothesis of an inhibition acting directly upon the cortical neuronal networks can not be rejected with certainty, but it is impossible at the present time to recognize the functional significance of such a process of supression in the arousal. Another difficulty results from the fact that our knowledge of inhibitions located in the cortex is too incomplete.

In the observations where a subcortical origin of the suppression (that of the spontaneous discharge of a cortical unit) has been eliminated, the inhibitory process probably acted upon the cortical interneurons the activity of which was necessary for the maintenance of the discharges of the pyramidal cell under observation (1). The observation by Whitlock, Arduini and Moruzzi (20) of a suppression in the arousal of the corticofugal discharges associated with spindles could also represent the effect of a dissolution of a functional organization. This would not necessarily involve the participation of a direct inhibition of cortical neurons in the arrest of the discharges.

The explanatory hypothesis that we suggest is based upon the duality of the effects that are exercised by the ascending reticular impulses upon the cortical interneurons: 1) a subliminal modification of their excitability responsible for the facilitation and 2) a supraliminal excitation able to block the specific sensory impulses by occlusive convergence. This inhibitory convergence could obtain the upper hand over the facilitating effect if the afferent specific test impulses do not have the synchronism (the density) that would permit them to surmount the partial refractiveness of the

interneurons that are activated above the threshold by arousal impulses. This would be the case for volleys originating from the peripheral receptors. Two experimental findings may be able to support such an interpretation. The intensification of the reticular, particularly of the thalamic stimuli, may result in a transformation of the facilitation by masking. On the other hand, the facilitating effect of the reticular ascending impulses may be dissociated from the desynchronizing effects upon the electrocorticogram (6, 9). If this dissociation is produced by atropine in large doses, the response of the acoustic area to clicks is not only no more reduced during the stimulation of the reticular formation, but may even be reinforced. All this takes place, it seems, as if under these conditions there would persist only the subliminal and facilitating effects of the arousal impulses upon the neuronal transmissions of the cerebral cortex.

The question arises regarding the functional significance of the experimental data. The test stimuli used for demonstrating the reticular facilitation evidently are not those which normally induce the functioning of the visual, auditory and somaesthetic areas. Click stimuli and ultrashort flashes hardly are more physiologic, although they represent stimuli applied to the receptors. These considerations let us foresee that inferences from observations in animals to psychophysiological experiences can only be made with the greatest caution. Yet Fuster's observations in the ape have demonstrated an experimental finding that is in good agreement with the concept of a reticular facilitation of cortical mechanisms. In these experiments, the stimulation of the reticular mesencephalic formation accelerated the visual recognition of objects that were presented tachistoscopically to the trained animal. In contrast, Rosenblith (19) found the auditory threshold to a click-stimulus lower in the drowsy than in the waking human subject. This contrast points to the necessity of distinguishing the relatively simple neurophysiologic processes that condition the conscious sensitivity to an elementary stimulus, from perceptual operations that are infinitely more complex and are related to the discrimination of structured stimuli.

It is not without interest to point out in this connection that the increase of voltage of an evoked potential represents only one of the aspects of the reticular facilitation of arousal. Another characteristic of this facilitation, particularly evident in the case of evoked auditory potentials, is the acceleration of the intracortical processes that are responsible for it. This acceleration is revealed by the more rapid succession of surface positive (hypothetically axosomatic) and surface negative phases (axo-dendritic) of the response. This acceleration is shown in Figure 1 for the response of the auditory area to a shock applied to the medial geniculate body. It can still be observed in the case where the evoked potential, caused this time by a click, is reduced in amplitude in the reticular or sensory arousal (Figure 1, J).

Two experimental findings may also aid in the functional interpretation of the masking phenomenon. One is the fact that the reduction of the response to a click is accompanied in arousal by an intensification of the rapid afterdischarge that one may put on a par with an arousal of the sensory cortex (2).

The other fact, without doubt more significant, is the observation by Li (17) that the number of the unit spikes that constitute the axon discharges of a cell of the somaesthetic area was increased (from 3 to 5) if the response of this cell to a shock applied to the thalamic relay nucleus was conditioned by a preceding volley of nonspecific impulses originating in the nucleus centro-medianus. It is remarkable that this interference at the same time had the effect of greatly reducing the amplitude of the specific evoked potential that was recorded

by means of a surface electrode. The depression of this evoked potential that represents a statistical average can coincide with the distinct dynamogenesis of a unit cell reaction. The intensification of the axon discharge of neurons that continue, in the reticulocortical arousal, to respond to specific afferent impulses could compensate and even overcompensate the numerical reduction of cortical cells, the supraliminal excitation of which by ascending reticular impulses would have made them relatively refractory to the sensory stimulation.

This short study of the questions which arise in the electrophysiologic studies of the processes of cerebral arousal, has attempted to demonstrate not only the satisfactory progress toward their explanation, but also the gaps in our knowledge of these problems, the fundamental importance of which is emphasized by the advent of psychopharmacology.

REFERENCES

1. Branch, C. L. and Martin, A. R. Inhibition of Betz cell activity by thalamic and cortical stimulation. J. Neurophysiol., **21**: 380–390, 1958.
2. Bremer, F. Les réactions auditives de l'écorce cérébrale. L'année psychologique, 1951, pp. 115–128.
3. Bremer, F. *Méchanismes de facilitation des transmission nerveuses centrales.* Masson, Paris. In press.
4. Bremer, F. and Stoupel, N. Etude des méchanismes de la synergie bioéletrique des hémisphères cérébraux. Acta physiol. et pharmacol. neerl., **6**: 487–496, 1957.
5. Bremer, F. and Stoupel, N. Etude pharmacologique de la facilitation des réponses corticales dans l'éveil réticulaire. Arch. internat. de pharmacodyn. et de thérap., **122**: 235–248, 1959.
6. Bremer, F. and Stoupel, N. Facilitation et inhibition des potentiels évoqués corticaux dans l'éveil cérébral. Arch. internat. de physiol., **67**: 240–275, 1959.
7. Buser, P. Activités de projection et d'association du neocortex cérébral des mammifères. I. Activitiés d'association et d'élaboration. Projections non spécifiques. J. de physiol., **40**: 589–656, 1957.
8. Creutzfeld, O. and Akimoto, H. Convergenz und gegenseitige Beinflussung von Impulsen aus der Retina und den unspecifischen Thalamus-kernen an einzelnen Neuronen des optischen Cortex. Arch. Psychiat. u. ges. Neurol., **196**: 520–538, 1958.
9. Dell, P. Discussion of the communication of Bremer at the International Colloquium on EEG of Higher Nervous Activity, Moscow, October, 1958.
10. Desmedt, J. E. and La Grutta, G. The effect of selective inhibition of pseudocholinesterase on the spontaneous and evoked activity of the cat's cerebral cortex. J. Physiol., **136**: 20–40, 1957.
11. Dumont, S. and Dell, P. Facilitations spécifiques et non spécifiques des réponses visuelles corticales. J. de physiol., **50**: 261–264, 1958.
12. Gauthier, C., Parma, M. and Zanchetti, A. Effect of electrocortical arousal upon development and configuration of specific evoked potentials. Electroencephalog. & Clin. Neurophysiol., **8**: 237–243, 1956.
13. Gellhorn, E., Koella, W. P. and Ballin, H. M. Interaction on cerebral cortex of acoustic or optic with nociceptive impulses. J. Neurophysiol., **17**: 14–21, 1954.
14. Gellhorn, E., Koella, W. P. and Ballin, H. M. The influence of hypothalamic stimulation on evoked cortical potentials. J. Psychol., **39**: 77–88, 1955.
15. Hunt, C. C. Monosynaptic reflex response of spinal motoneurones to graded afferent stimulation. J. Gen. Physiol., **38**: 813–852, 1955.
16. Jasper, H. H. and Ajmone-Marsan, C. Thalamocortical system and electrical activity of the brain. Fed. Proc., **7**: 6, 1958.
17. Li, C. L. The facilitatory effect of stimulation of a thalamic nucleus on cortical sensory neuronal responses. J. Physiol., **131**: 115–124, 1956.
18. Moruzzi, G. and Magoun, H. W. Brain stem reticular formation and activation of the electroencephalogram. Electroencephalog. & Clin. Neurophysiol., **1**: 455–473, 1949.
19. Rosenblith, W. Personal communication.
20. Whitlock, D. G., Arduini, A. and Moruzzi, G. Microelectrode analysis of pyramidal system during transition from sleep to wakefulness. J. Neurophysiol., **16**: 414–429, 1953.

SOUND LOCALIZATION IN INFANCY

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The cradle of American Neurology was Philadelphia, for here S. Weir Mitchell began his perceptive clinical studies and was followed by a distinguished galaxy of disciples. Dr. Spiegel represents the best traditions of neurology not only for Philadelphia but for all of these United States. His investigations have been inclusive of the total gamut of neurologic disciplines and, like the founder of American neurology, S. Weir Mitchell, his studies show a remarkable insight into neurophysiological principles.

It is a privilege to be invited to participate in this Festschrift and to recall the happy days of our Philadelphia lives and the impact which Dr. Spiegel had upon us in our formative days. Recalling those remarkable studies of Dr. Spiegel on vestibular function and temporal localization (22) we consider it timely to present as a tribute to him our clinical studies on temporal lobe function in infants.

The bedside testing of patients with temporal lobe disease is often frustrating. Temporal lobe types of aphasia are, of course, quite definitive, but appear only when the dominant hemisphere is involved. Facial weakness occurring in a patient with temporal lobe disease means that the disease process has invaded the capsular area. Likewise, involvement of visual fields, while highly definitive, means that the lesion has progressed so deeply in the temporal lobe that the periventricular white matter is involved. Studies of music appreciation deficiencies are not highly diagnostic for anterior temporal lobe lesions. Audition is not impaired to a sufficient degree in patients with temporal lobe disease to be of clinical significance. Yet at the bedside the description of temporal lobe seizure types and the presence of the peculiar temporal lobe personality changes strongly suggest a temporal lobe disease. It is in such instances where sound localization may be of value in arriving at a diagnosis of temporal lobe disease, for the ability to localize sound in space is ofttimes impaired on the side opposite the temporal lobe lesion.

This inability to localize sound in space-dysteriophonia is a significant sign in adults. The validity of this sign in children, however, is not known. Infants at birth and shortly thereafter quite obviously have difficulty in localizing sound in space. This study was designed to determine the age at which normal infants can localize sound in space.

METHODS

The auditory localization tests were carried out on 26 infants ranging from two to forty-nine weeks of age. All infants studied were free of neurologic disease. Most of the infants were from the Well Baby Clinic and all had normal peri- and post-natal histories. A few infants were included who had normal peri- and post-natal histories but who had been hospitalized for acute enteritis. Otoscopic examination was normal in all. Each infant was tested at least twice. The series comprised 12 females and 14 males. All infants were awake when tested and all but three were "resting," these exceptions being irritable and fussy.

Testing consisted of placing the child in a regular hospital crib and applying a special frame over the crib. The frame consisted of three horizontal bars crossing from side to side over the crib and a vertical arm on each side. The infant was placed

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on its back so the intraaural line was on a line with the vertical bars. Buzzers were placed on the vertical arm at the level of the ear, and on the frame on top of the crib, one at the level of the bridge of the nose (midline anterior), one near the feet of the infant (midline inferior) and one above the head (midline superior). The distance from the head to the frame above the crib was 17.5 inches. All five buzzers had identical pitch and intensity. The buzzers were activated by panel switches out of the infant's range of vision and each buzzer was activated for a five-second period.

Extraneous stimuli were controlled by limiting the number of people present to the examiners; the examiners themselves remained out of the line of vision. Lighting also was kept constant, as were other sound stimuli.

RESULTS

All twenty-six normal infants tested responded to an auditory stimulus either reflexly or reflexly together with a learned response. It is thus apparent that none of these children had an impairment of hearing which could have interfered with the test.

Table 1 presents the reflex responses of the infants to the auditory stimuli. The auro-palpebral reflex (eye-blink response) is defined as a closing of the eyelids if the eyes are open, and tightening of the lids if the eyes are closed. The acoustic muscle reflex is defined as a sudden generalized flexing movement of the body or part of the body in response to a sudden sound. The auditory oculogyric reflex is defined as a movement of the eyes to a sudden sound. Each reaction was rated on a one to four plus basis; one plus indicating that the reaction occurred from a sound stimulus in only one position, and four plus when it was elicited by sound stimuli in four or more positions. A negative rating was given when no response was obtained from sound stimuli from any of the positions.

TABLE 1

Auditory Reflex Responses in Infancy

Case No.	Age (wks)	Sex	APR	AMR	AOR
1	2	F	+	++++	−
2	4	M	+	++	−
3	8	M	++	+	+
4	14	M	−	+++	+++
5	16	F	++	++	−
6	18	M	−	++++	++++
7	19	F	++++	++++	++++
8	22	M	−	++++	++++
9	22	F	−	++++	+++
10	26	F	+	+	+
11	26	F	++	++	++
12	27	F	−	++++	++++
13	28	F	−	++++	++++
14	28	F	−	++	+++
15	32	F	−	+	++
16	34	F	−	+++	+++
17	36	M	−	++++	++++
18	36	F	−	−	++++
19	36	M	−	+	++
20	36	F	−	++	+++
21	37	M	−	++++	+++
22	38	F	+	+	+
23	39	M	−	++++	++
24	40	M	−	++++	+++
25	48	M	−	++++	++
26	49	M	+	+	−

APR: Auro-Palpebral Reflex
AMR: Acoustic Muscle Reflex
AOR: Auditory-Oculogyric Reflex

The acoustic muscle reflex (startle reflex) occurred in twenty-five of the twenty-six infants studied. This reflex reaction consisted of a generalized sudden flexion movement of the extremities or extremity and occasionally only of the facial and neck muscles. It is interesting to note that the reflex was found to be present as frequently in the oldest subject as well as the youngest. Some authors have felt that the sound reflex reactions diminish as the child approaches the age of one year (4), while others have maintained that auditory reflex responses persist throughout life (7, 8).

Twenty-two (85 per cent) of the infants responded to a sound stimulus with an extra ocular muscle reaction. The auditory oculogyric reflex in this series is defined

TABLE 2

Localization of Sound Source in Different Air Ranges

Case No.	Age (wks)	Right lateral position	Left lateral position	Midline anterior position	Midline inferior position	Midline superior position
1–7	2–19	−	−	−	−	−
8	22	+	+	−	−	−
9	22	−	−	−	−	−
10	26	−	−	−	−	−
11	26	+	+	−	+	−
12	27	+	+	+	−	−
13	28	−	+	+	−	−
14	28	+	+	−	−	−
15	32	+	−	+	−	−
16	34	+	+	+	−	−
17	36	+	+	−	+	−
18	36	+	+	+	+	+
19	36	+	+	+	−	−
20	36	+	+	−	−	−
21	37	+	+	−	−	+
22	38	−	−	+	−	−
23	39	+	+	+	+	−
24	40	+	+	−	−	−
25	48	+	+	+	+	+
26	49	+	+	+	−	+

as a movement of the eyes to a sudden sound. The direction of the movement of the eyes in this reflex has not been clearly defined. It has been maintained that the movement is towards the sound (3) as well as in the opposite direction (6). As observed in this series, the reaction of the eyes have primarily been a roving movement in a horizontal plane. This reflex appeared consistently in infants over four months of age.

About one-third of these infants (nine) responded with the auro-palpebral reflex. This reflex was seen more frequently in the infants up to five months of age. It was, however, also observed in the older infants.

All of the infants responded with at least one of the reflex reactions. Twenty-five responded to the sound stimulus with two or more reflexes, and twenty-one (81 per cent) responded with two reflex responses. The one subject who responded with only one reflex revealed a consistent oculogyric reflex.

The ability to localize sound in each position was considered present only if the head and eyes of the infant turned towards the source of the sound. When present, this reaction was very definite and easily recognizable, with an occasional infant reaching out to the sound source.

All of the infants over twenty-six weeks of age, in number fifteen, showed a definite ability to localize sound in at least one of the positions tested (Table 2). (Only one infant under twenty-six weeks of age could do this.) All but one of them could localize sound when the source was in a direct line to either the right or left ear. Of these fifteen, twelve infants could localize sound in both these directions. Ten infants localized sound from the midline-anterior position. The other two positions were not localized as well.

DISCUSSION

Neurophysiologic experiments have long given evidence of the temporal lobe function in localization of sound. Jacobsen and Elder (10) demonstrated in 1936 that in a trained baboon temporal lobectomies decreased the ability to localize sound in space. Rosenzweig (18) and Tunturi (25) noted a spatial arrangement in temporal lobe cortex when evoking potentials by auditory stimulation. Pennington (15) and Neff *et al.* (13, 14) noted that after bilateral ablations of the auditory cortex in animals trained to respond to auditory cues, there was a marked loss in ability to retain the learned response based on the spatial localization of sound. These authors found, however, that a unilateral ablation did not produce the same results. Sanchez-Longo and Forster (20) were able to reproduce, by temporal ablations in monkeys, difficulty in localizing sound on the side opposite the ablation.

The clinical literature contains a number of articles concerning the localization of sound. Case reports (5, 9) and methods of testing this function have been described. The case reports describe patients with lesions in the area of the temporal lobe,

having a subsequent diminished ability to localize sound.

Several authors have developed methods for testing sound localization (2, 9, 19, 21). Bocca *et al.* (2) tested "cortical" hearing on the theory that the correct perception of sound should involve psychic integration. This was done by fractioning a verbal message with a periodic commutator and sending each fraction to alternate ears. A number of patients with tumors in the region of the temporal lobe had an asymmetric articulation score, the score being lower in the ear contralateral to the lesion.

Sanchez-Longo, Forster, and Auth developed a new clinical test for sound localization using a Maico H I model audiometer and a Feree-Rand type of perimeter (21). In this procedure one of the receivers of the audiometer is placed on the perimeter and the masking tone turned on. The blindfolded subject is then asked to localize the source of the sound. Impairment of sound localization was found in the countralateral ear in patients with temporal lobe lesions.

In children sound localization has been studied primarily in terms of the detection of deafness (4, 27). Ewing and Ewing (4), using voice, percussion toys, pitchpipes and meaningful sounds, tested a group of children whose ages ranged from birth to five years of age in order to determine the type of sound to which a child will react. It was noted that the capacity to locate the source of sound is well developed at the end of the first year, and it was concluded that the child who does not turn his eyes or head towards a familiar person calling his name in a modulated voice is severely or totally deaf.

This importance of the early detection of deafness was the stimulus for this type of investigation. As a rule hearing tests in the newborn have been limited to the observation of reflex responses to a cowbell, whistles, tuning forks, etc. as a stimulus (4, 6, 17, 24, 27). Various modifications have been used. Wedenberg (26) used a pure tone audiometer with various frequency outputs and observed the reflex responses in the newborn infant. Psychogalvanic skin reflex have been used for the detection of deafness in young children (1, 23) but its value has been limited with very young infants. The changes of the electroencephalographic tracings have been those of a non-specific arousal pattern (11, 12, 16).

In view of the disappointing results for the detection of hearing impairment in the newborn and infancy period by a single test, the ascertainment of deafness, then, depends on information gathered from a series of tests, including the clinical data. The ability to localize sound must be an integral part of this series and should continue to be emphasized in evaluating infants over six months of age.

The evidence that sound localization is a function of the auditory area of the temporal lobe in adults is convincing. After the first six months of life this response becomes well developed and presumably remains so. The ability to localize sound is accordingly an excellent additional criterion in the determination of the normal as well as pathologic pattern of growth and development of the temporal lobe.

This relatively simple test for sound localization may well serve in the battery of tests for determining the ability to hear, especially in children over the age of four months. However, we believe this test may be of much greater significance in the neurologic examination than in the audiologic. It is quite possible that a unilateral inability to localize sound may prove to be a significant and early diagnostic test for temporal lobe disease. To test this hypothesis we intend to continue these studies on children who have suffered specific brain damage and also on children with the various forms of mental retardation.

SUMMARY

Normal infants at the age of 26 weeks develop the ability to localize sound in

space. The clinical significance of this function is discussed.

REFERENCES

1. Barr, R. Pure tone audiometry for pre-school children. Acta oto-laryng., Supp. **121**, 1955.
2. Bocca, E. Calearo, C., Cassinari, V., and Migliavacca, F. Testing "cortical" hearing in temporal lobe tumors. Acta oto-laryng., **45**: 289–304, 1955.
3. DeJong, R. H. *The Neurologic Examination,* pp. 148–278. Hoeber, New York, 1950.
4. Ewing, T. R. and Ewing, A. W. G. The ascertainment of deafness in infancy and early childhood. J. Laryng. & Otol., **59**: 309–333, 1944.
5. Frazier, C. H. and Rowe, S. M. Certain observations upon localization in fifty-one verified tumors of the temporal lobe. A. Res. Nerv. & Ment. Dis., Proc., **13**: 251–258, 1934.
6. Froeschels, E. Testing the hearing of young children. Arch. Otolaryng., **43**: 93–98, 1946.
7. Galambos, R., Rosenberg, P. E. and Glorig, A. Eyeblink response as a test for hearing. J. Speech & Hearing Disorders, **18**: 373–378, 1954.
8. Galloway, F. T. and Butler, R. A. Conditioned eyelid response to tone as objective test of hearing. J. Speech & Hearing Disorders, **21**: 47–55, 1956.
9. Greene, T. C. Ability to localize sound, study of biaural hearing in patients with tumors of the brain. Arch. Surg., **18**: 1825–1841, 1929.
10. Jacobsen, C. F. and Elder, J. H. Studies of cerebral function in primates. II The effects of temporal lobe lesions on delayed responses in monkeys. Comp. Psychol. Monogr., **13**: 61–65, 1936.
11. Marcus, R. E. Hearing and speech problems in children. Observations and use of electroencephalography. A.M.A. Arch. Otolaryng., **53**: 134–146, 1951.
12. Marcus, R. E., Gibbs, E. L. and Gibbs, F. A. Electroencephalography in diagnosis of hearing loss in very young children. Dis. Nerv. System, **10**: 170–173, 1949.
13. Neff, W. D. and Yela, M. Function of the auditory cortex, the localization of sound in space. Am. Psychologist, **3**: 243, 1948.
14. Neff, W. D., Fisher, J. F., Diamond, I. T. and Yela, M. Role of auditory cortex in discrimination requiring localization of sound in space. J. Neurophysiol., **19**: 500–512, 1956.
15. Pennington, L. A. Function of the brain in auditory localization: II. Effect of cortical operation upon original learning. J. Comp. Neurol., **66**: 415–442, 1937.
16. Perl, E. R., Galambos, R. and Glorig, A. The estimation of hearing threshold by electroencephalography. Electroencephalog. & Clin. Neurophysiol., **5**: 501–512, 1953.
17. Richmond, J. B., Grossman, H. J. and Lustman, S. L. A hearing test for newborn infants. Pediatrics, **11**: 634–638, 1953.
18. Rosenzweig, M. R. Cortical correlates of auditory localization and of related perceptual phenomena. J. Comp. & Physiol. Psychol., **47**: 269–276, 1954.
19. Sanchez-Longo, L. P. and Forster, F. M. Clinical significance of impairment of sound localization. Neurology, **8**: 119–125, 1958.
20. Sanchez-Longo, L. P. and Forster, F. M. Unpublished data.
21. Sanchez-Longo, L. P., Forster, F. M. and Auth, T. L. A clinical test for sound localization and its application. Neurology, **7**: 655–663, 1957.
22. Spiegel, E. A. Labyrinth and cortex. The electroencephalogram of the cortex in the stimulation of the labyrinth. Arch. Neurol. & Psychiat., **31**: 469–482, 1934.
23. Stewart, K. C. Some basic considerations in applying the G.S.R. technique to the measurements of auditory sensitivity. J. Speech & Hearing Disorders, **19**: 174–183, 1954.
24. Stubbs, E. M. The effects of the factors of duration, intensity, and pitch of sound stimuli on the responses of newborn infants. Univ. of Iowa Studies, **9**: 4, 1934.
25. Tunturi, A. R. A study of the pathway from the medial geniculate body to the acoustic cortex in the dog. Am. J. Physiol., **147**: 311–319, 1946.
26. Wedenberg, E. Auditory tests in newborn infants, Acta oto-laryng., **46**: 446–461, 1956.
27. Wichart, D. E. S. The hard of hearing infant. Ann. Otol. Rhin. & Laryng., **63**: 378–393, 1954.

CARDIOVASCULAR PHENOMENA DURING SEIZURE ACTIVITY

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Epileptic attacks are very often accompanied by cardiovascular alterations, such as flushing of the face, increase in blood pressure and modifications of heart rhythm. In visceral seizures some of these symptoms may be the principal manifestations of illness. In motor epilepsy, correlations between clinical symptoms and anatomical localization of afterdischarges have been demonstrated. Movements have a systematic representation in the cerebral cortex, and study of the onset and pattern of motor phenomena often indicates which cortical areas are responsible for the initiation of the epileptic attack. Autonomic representation is also known to exist in the cerebral cortex and in deeper structures, but systematization is not clear and only a few studies have established precise relations between cerebral afterdischarges and cardiovascular phenomena. Recently, Andy *et al.* (1), working with unanesthetized cats, have shown that blood pressure depression invariably accompanied amygdaloid afterdischarges, but a rise of blood pressure was observed when seizure activity propagated to the hippocampus and fornix. Heart rate and rhythm were usually undisturbed. Morin *et al.* (12), working with curarized dogs, claimed that the spread of epileptic discharges evoked by cerebral stimulation was responsible for the increase of blood pressure, and they related the pattern and shape of the hypertension to the character and duration of the epileptic spread. However, evidence of the independence of cardiovascular effect from epileptic phenomena is strongly supported by the experiments of Hoff and Green (7) and Kaada (9), because pressor effects were evoked by cortical stimulation below motor thresholds, and were also obtained in curarized animals. As electrical activity of the brain was not recorded, afterdischarges could exist without clinical manifestations. Cardiovascular effects evoked by cerebral stimulation have been described by Hess (6), and Spiegel and Hunsicker (16). See also summaries in Folkow (5), McDowall (9) and Rushmer and Smith (15). Most investigators used animals under anesthesia, which probably was largely responsible for the great variability of results. Some barbiturates, such as Thialbarbitone, cause a marked alteration in the EKG, as shown by Mihailović *et al.* (11). Cases of epilepsy in humans have been described showing cardiac disturbances as the main manifestation. These cases were successfully treated by antiepileptic medication (Janjigian [8], Phizackerly *et al.* [13]). The present study was made with cats, monkeys and humans with intracerebral electrodes and without anesthesia. The purpose was to investigate correlations between seizure activity and cardiovascular phenomena.

METHODS

Ten rhesus monkeys, six cats and nine patients were used. From 14 to 30 electrodes were permanently implanted in the brain of each subject, according to methods pre-

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FIG. 1. Twelve intracerebral contacts and one intraaortic cannula were permanently implanted in the cat. Blood pressure was recorded with a transducer mounted on a harness. Thus it was possible to make a long-term study of cerebral-cardiovascular correlations in unanesthetized, unrestrained animals.

viously described (2). Electrical activity of the brain was recorded by a Model III-D, 8-channel Grass instrument. In monkeys and in humans, two synchronized machines with a total of 16 channels were used. EKG and often respiration were also recorded. A S-4 Grass stimulator was used. The usual parameters were 100 cps., 0.2 msec. of pulse duration and five seconds of total stimulation time. Monopolar and bipolar stimulations and recordings were used. Voltage and milliamperage of stimulations were simultaneously monitored during the experiments by a dual beam Du Mont oscilloscope. In the cats, a polyethylene tubing (PE-50) filled with heparin was permanently introduced up to the aorta through the femoral artery. The other end of the tubing was sealed by heat and passed below the skin of the thigh up to the back of the animal, where it was protected by a bandage. To make the blood pressure recordings, the sealed end was opened, attached to a transducer carried by the animal, and connected electrically to a Hathaway recorder. After each experiment the tubing was again sealed by heat. Such a preparation was in good working condition for weeks (Figure 1). After the study was completed, cats and monkeys were sacrificed under anesthesia, perfused with formaline; the brain was removed and sectioned to determine histologically the location of the contacts.

Additional data about EKG activity during spontaneous and evoked afterdischarges was obtained in a group of seven schizophrenic and two epileptic patients who had electrodes implanted for several days in frontal and temporal lobes respectively. More information about these patients has been published elsewhere (3).

RESULTS

Relation between motor effects and blood pressure in the cat. Spontaneous irregular changes of blood pressure were observed for several hours if anesthesia had been given, even when small doses of pentothal (4 mg. per kg.) were used for a short time

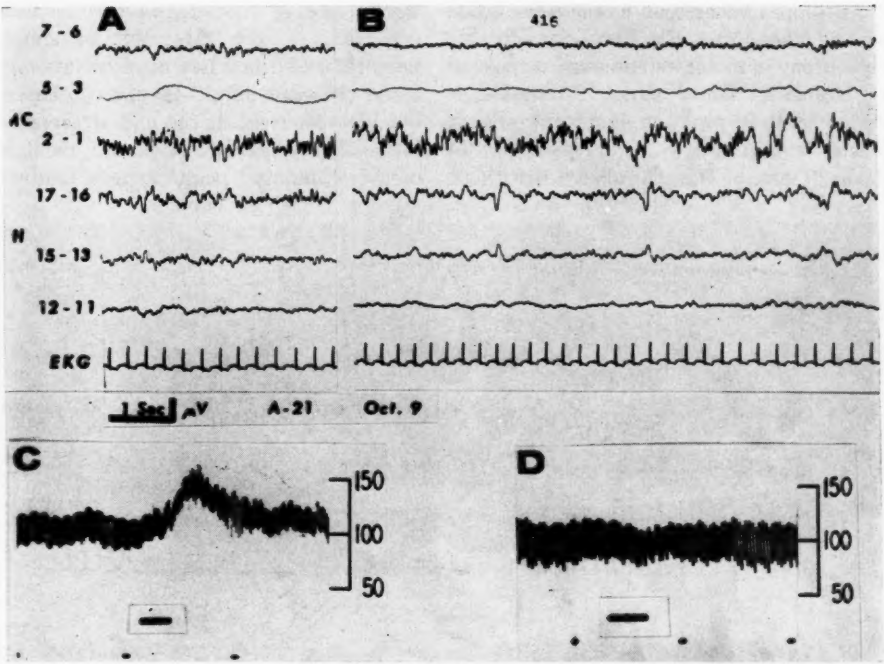

FIG. 2. (A): Control. (B): Electrical activity during the rise of blood pressure shown in (C) was not modified. (C): Stimulation of left cruciate sulcus (Contact #7) produced flexion of the right hind limb and increased the blood pressure. (D): Stimulation of Contact #6, located on white substance 3 mm. below Contact #7, evoked a similar flexion of the right hind limb and a small drop in blood pressure.

Note: Location of contacts for Figures 2 and 3: MC7, sulcus cruciatus; #6, white substance; #5 and #3, sulcus presylvius; #2, inferomedial pathways from sulcus presylvius; #1, orbital cortex, H #17: corpus callosum, #16, nucleus lateralis dorsalis; #15, nucleus lateralis posterior; #13, centre median; #12, red nucleus—centre median; #11, substantia nigra. Contacts #4 and #14 correspond to the indifferent electrodes.

Time signal for all blood pressure recording: 15 seconds at bottom line; next upper line: stimulation signal.

(about 10 minutes). For this reason, most of the experiments were carried on after a recovery period of at least 48 hours.

During the experiments the cats lay peacefully and, from time to time, they licked themselves, looked around, or walked about in the small observation cage (Figure 1). Spontaneous activity did not significantly modify the blood pressure, which was held steady with only minor variations. Electrical stimulation of the gyrus proreus and of the cortex hidden within the sulci presylvius, coronalis and cruciatus, evoked contralateral and well-organized movements, similar to those observed during spontaneous activity of the animal. The pattern of evoked movement was reliable through months of experimentation.

With respect to vascular responses, stimulation of the same point gave reliable results, but different points of motor areas gave the following effects. 1) *Pressor responses* (Figure 2C): With a delay of 2 to 5 seconds, the blood pressure began to rise, reaching a peak a few seconds after the end of the stimulation and returning to normal a few seconds later. The evoked motor effect appeared after a delay of 1 to 2 seconds,

and disappeared as soon as the stimulation ceased. There was, therefore, considerable asynchrony in motor and pressure responses. At intensities below motor thresholds, it was difficult to produce significant pressor effects, but, in a few instances, a rise of about 20 mm. of Hg. was observed without accompanying movements. 2) *Depressor responses* (Figure 2D): Almost simultaneously with the onset of stimulation, the blood pressure fell 10–20 mm. of Hg. and quickly recovered at the end of the stimulation. 3) *No pressure response:* about half of the stimulated points gave a motor re-

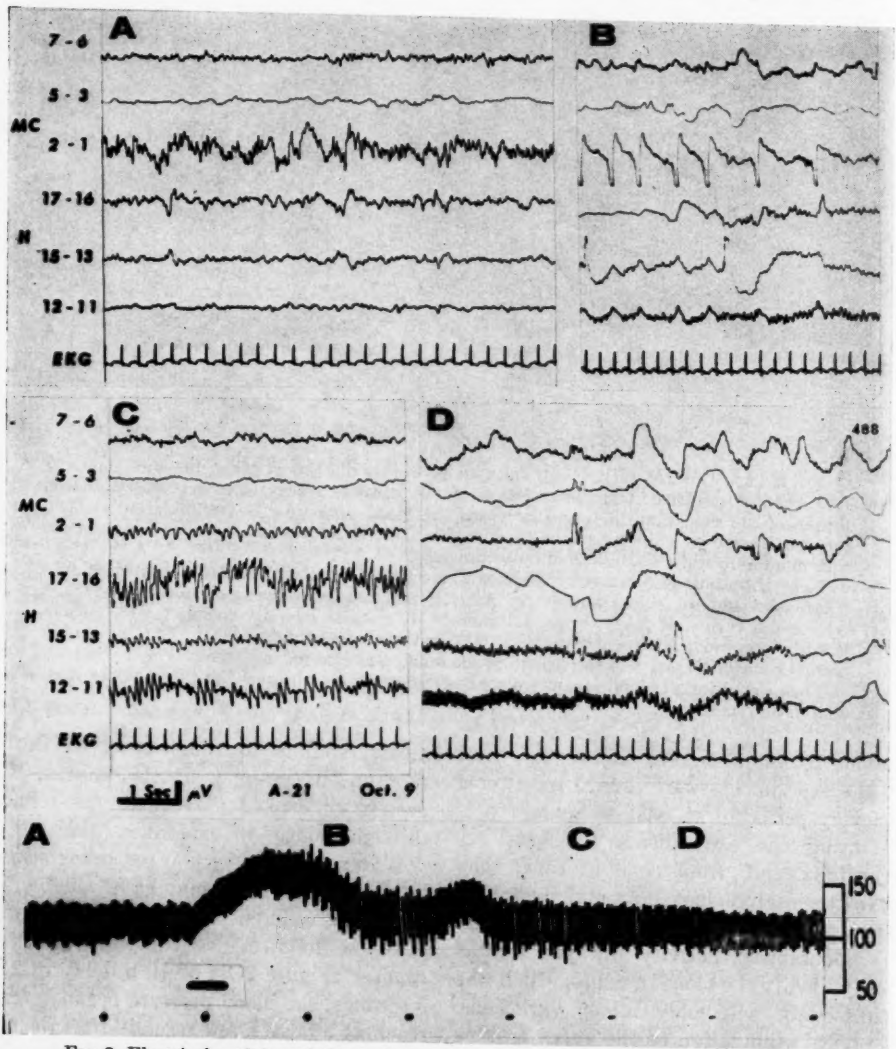

FIG. 3. Electrical activity of the brain is shown at different times during blood pressure response evoked by stimulation of the orbital cortex in the cat. Increase of blood pressure was coincident with afterdischarge in leads 2–1 and twitching in the face (B). Seizure activity localized in thalamic and substantia nigra contacts (C and D) did not affect blood pressure.

sponse without any observable change in the blood pressure.

Pressor, depressor and neutral points were distributed with no apparent anatomical systematization. As cardiovascular responses are certainly well organized, it is likely that there exists a functional organization, through connecting pathways. As indicated by the EKG (Figures 2A and B), the rhythm of the heart was not modified by motor cortex stimulation, but a small acceleration often accompanied the evoked rise of blood pressure. The described pressor and motor responses were observed without any modification of the electrical activity of the brain, as recorded from the stimulated points, neighboring motor areas and also from thalamic nuclei (Figures 2A and B).

Relation between seizure activity and blood pressure in the cat. Electrical stimulation of the *orbital cortex* easily produced localized afterdischarges accompanied by convulsive manifestations, usually limited to the contralateral side of the face, with twitching of the eye, ear and facial musculature. Motor phenomena were accompanied by high voltage spikes of rather low frequency—around 1–3 per second—sychronous with the motor facial contractions. Electrical and motor phenomena often remained localized, especially if they were of short duration, but could last as long as 40 seconds, in which case seizure activity usually spread to other areas. Increase of blood pressure always accompanied the orbital cortex afterdischarge (Figures 3 and 4). The rise began with some delay after the onset of stimulation; reached a peak several seconds after the stimulation ended; and remained high, with only a small decline, as long as the afterdischarge lasted. As the motor component was rather small in the orbital cortex seizures, the rise in blood pressure should not be interpreted as a result of muscular activity, but rather as a direct vasomotor effect due to neuronal discharge.

In one cat the evoked afterdischarges propagated from the orbital cortex to the thalamus and to the substantia nigra, with persistence of independent foci in these structures. Thus it was possible to evaluate, in one experiment, the participation of different areas of the brain in vasomotor reactions. As shown in Figure 3, electrical stimulation of Contact #1 produced a local afterdischarge which was accompanied by the usual twitching of the contralateral side of the face. This afterdischarge lasted

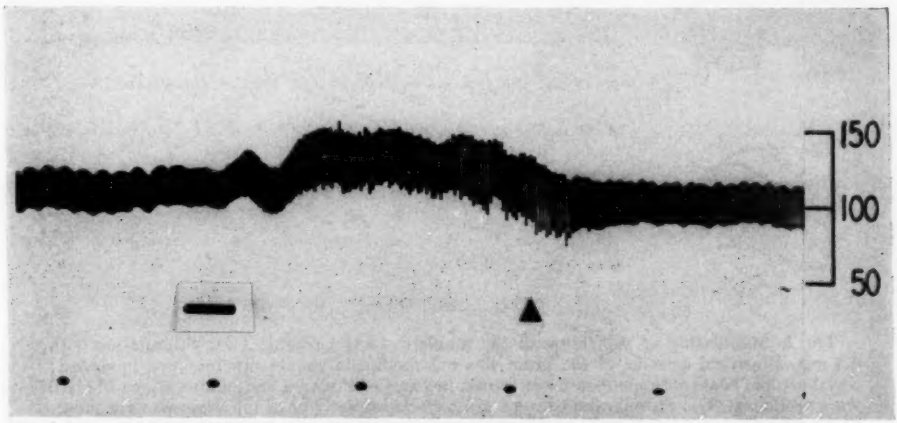

FIG. 4. Orbital cortex stimulation evoked a 30-second afterdischarge, localized in the stimulated area, with a pattern similar to Figure 3B. Blood pressure was kept high until the end of the afterdischarge, marked with ▲.

about 20 seconds and was coincident with a rise of blood pressure of about 50 mm. of Hg. High voltage activity was observed in the thalamus 10 seconds after the end of stimulation, and later also in the substantia nigra leads. It continued for a total of 58 seconds in leads 16–17 (nucleus lateralis dorsalis and corpus callosum—see Figure 3C), and for 70 seconds in leads 11–12 (substantia nigra, red nucleus and centre median—see Figure 3D). The different pattern and duration of each afterdischarge suggested the existence of three independent foci, which were triggered by the same electrical stimulation of the orbital cortex. The animal was out of contact only during the thalamic afterdischarge, when dilatation of the pupils and some automatism were observed. The cat uttered several meows and regained contact with his surroundings, responding to acoustic and visual signals immediately after the thalamic seizure ended, in spite of the continuation of the substantia nigra afterdischarge.

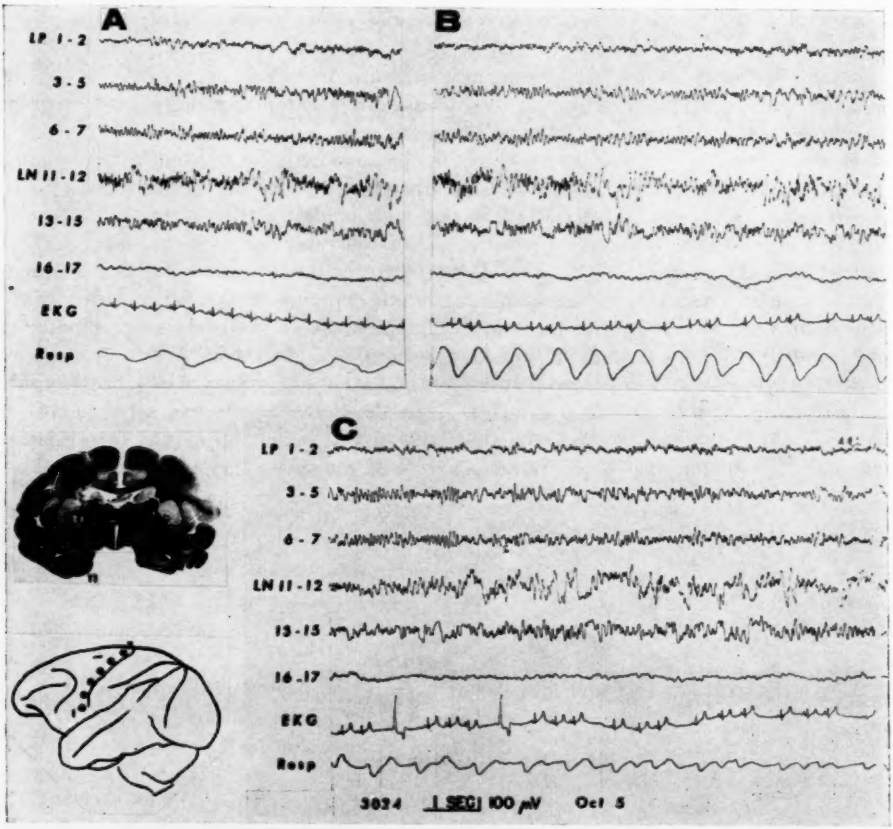

FIG. 5. Stimulation of subiculum in the monkey. (A): Control; (B): Stimulation with 1.8 mA. Electrical activity of the brain was not modified; respiratory rate was increased; atrial ectopic beats with compensatory pause, increase of P waves and modifications of QRS were produced. (C): Stimulation with 4.5 mA.: electrical activity of the brain was not modified; respiratory rate increased and was irregular; ventricular extrasystoles and later atrial ectopic beats were produced; records (B) and (C) shown five seconds after the end of stimulation.

The blood pressure increased only during the orbital cortex seizure, and returned to normal while the afterdischarges continued in the thalamus and in the substantia nigra. The heart rate was not modified during the stimulation or during the rise of blood pressure, but it slowed down during the recovery period, and the systolic diastolic amplitude increased. The blood pressure descended to the control level, apparently without being affected by the continuation of seizure activity in the thalamus and substantia nigra. Electrical stimulation of these two structures failed to produce any modification in the blood pressure. Stimulation of the orbital cortex with intensities just below afterdischarge thresholds also produced no pressor effect, which was always dependent on the presence of seizure activity in this area.

Cerebral structures which influence the EKG in the monkey. Electrical stimulation of the subiculum, posterior hippocampus and substantia nigra, with intensities below seizure threshold, produced consistent modifications in the EKG without disturbing the electrical activity of the brain. Figure 5 shows that stimulation of Contact #1 with 1.8 mA. increased the respiratory rate and modified the cardiac rhythm. Atrial ectopic beats followed by compensatory pause were observed every three heart beats, for about 30–50 seconds after the end of the stimulation, associated with some modification of P wave and QRS complex (elevation of S. T. segment and higher amplitude of the sharpened T wave). When intensity of stimulation was increased to 4.5 mA., the period of ectopic atrial beats had a similar duration, but was preceded by a few seconds of ventricular extrasystoles, as shown in Figure 5C. In this monkey, electrical activity of the brain was recorded by 30 different contacts located in both sides of the motor cortex, limbic system, and mesencephalon. No modification could be detected in any of them during the EKG disturbances. The pattern of the ventricular extrasystoles was typical for each of the stimulated structures. Thus the pattern shown in Figure 6A characterized posterior hypothalamic excitations, while the pattern shown in Figure 6B was typical for substantia nigra stimulation. This relation be-

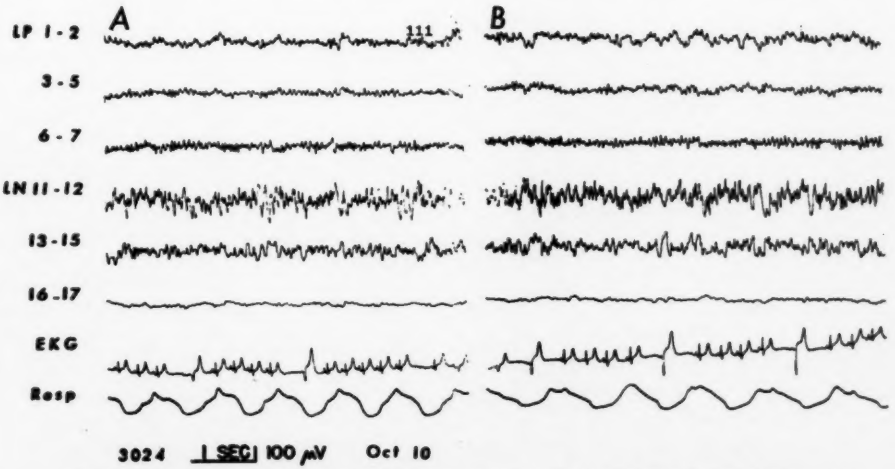

FIG. 6. Ventricular extrasystoles evoked by stimulation of posterior hypothalamus (A) and substantia nigra (B) had a different pattern than those evoked by stimulation of the subiculum (Figure 5C).

tween site of cerebral activation and EKG pattern indicates a specificity of effect which deserves further investigation.

On the other hand, electrical stimulation of motor and premotor cortex, nucleus basalis of the amygdala and nucleus dorsalis of the thalamus, did not affect cardiac function, even if the intensity of the stimulation was high enough to evoke paroxistic afterdischarges. This lack of electrocardiographic influence was especially impressive in the case of generalized motor seizures evoked by stimulation of Area 4 or 6, in which clonic convulsions were observed in all the body with electric afterdischarges recorded by all the intracerebral contacts, and only a small increase appeared in the heart rate without any other EKG modification.

In addition to these two groups of cerebral structures, one with, and the other without influence on the EKG, a third group could be considered, including areas such as the fornix and central gray, which did not modify the EKG when stimulated below seizure levels, but which produced extrasystoles when afterdischarges were evoked.

Stimulation of the central gray with 5 mA. for 5 seconds evoked an afterdischarge of 30–50 seconds duration which was transmitted to the reticular substance and contralateral motor cortex. Ventricular extrasystoles with a pattern similar to those of substantia nigra stimulation appeared for several seconds after the stimulation, and then a period of ectopic atrial beats outlasted for several seconds the duration of the afterdischarge. Intensities below this level failed to modify the electrical activity of the brain, or to produce EKG changes.

EKG during spontaneous and evoked seizures in humans. As documented by motion pictures and tape-recorded conversations, electrical stimulation of the orbital cortex in schizophrenic patients did not produce any clinical or psychological symptoms even if the applied intensity was strong enough to evoke a local afterdischarge of one or two minutes duration. Seizure activity shown in Figure 7, RE, was recorded while the patient was seated in an arm chair, discussing different subjects with the therapist. Skill of movement was not affected; no sensation was reported, and the EKG was not modified. It was interesting that this local afterdischarge had a high voltage in the orbital contacts, but could not be detected by standard scalp EEG leads (LP-RP).

In two epileptic patients, spontaneous bursts of 3 per second spike and wave activity involved most of the recording leads which were located on the surface and in the depth of both temporal lobes. These bursts lasted from a few seconds up to one minute or even longer, without any observable modification of the EKG, as shown in Figure 7, OC. No clinical symptoms were noticed during these attacks, but at times it seemed that changes in mood might possibly be related to the paroxystic activity, a problem which is being studied at present from records.

In one of the epileptics (HL) localized electrical afterdischarges were evoked by electrical stimulation of several of the contacts placed in the depth of the temporal lobe, but only when points RN 3–4 were stimulated was the evoked seizure activity accompanied by modification of the rhythm of the heart, which lasted 10–20 seconds. No ventricular extrasystoles were produced in any case, and stimulation below seizure threshold did not produce any EKG disturbance.

DISCUSSION

Correlation between anatomical location of seizure activity and cardiovascular manifestations was observed in cats, monkeys and humans. A correlation was found to exist between the site of cerebral stimulation and the pattern of evoked ventricular extrasystoles. Specificity of effects, therefore, seemed evident, as has been demonstrated by Andy *et al.* (1), who showed that afterdischarges localized in the amygdala

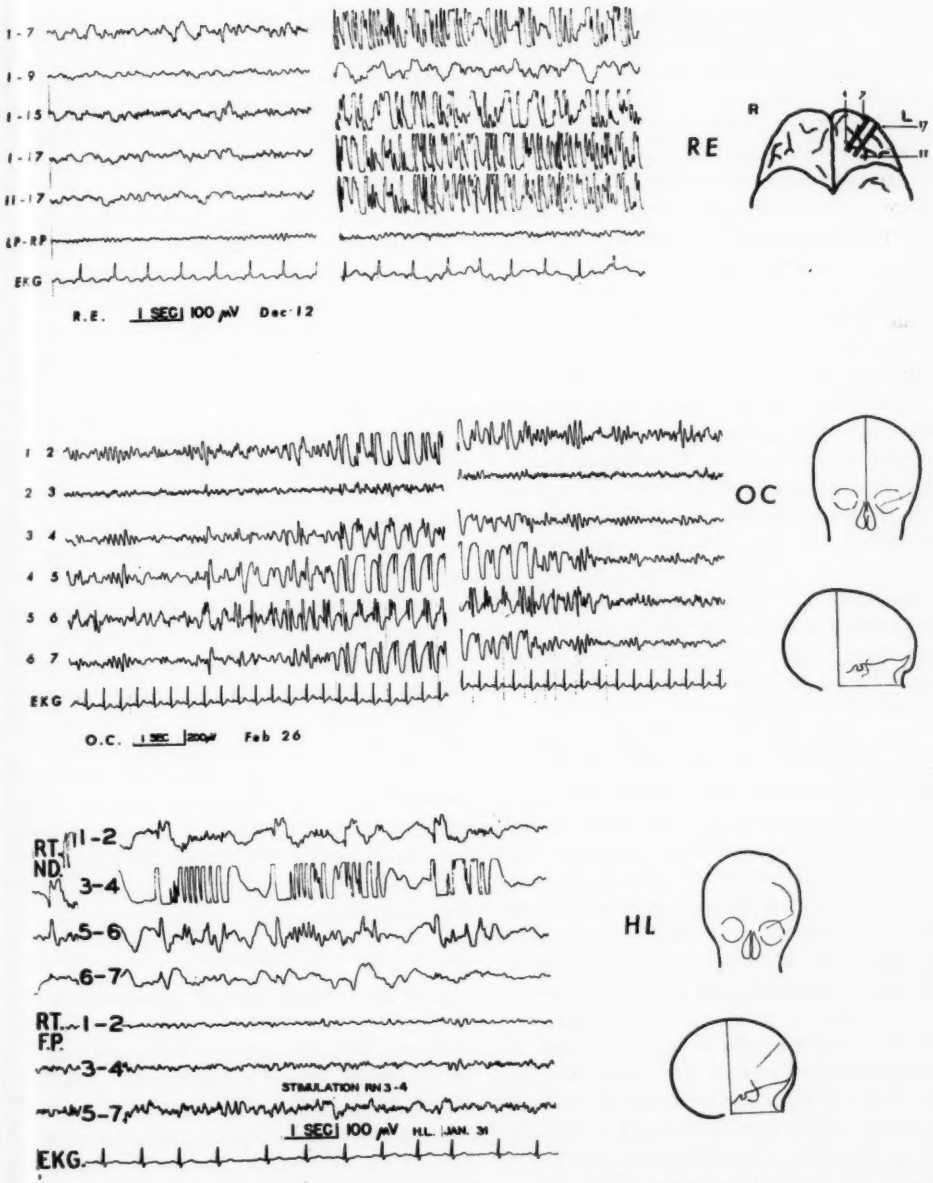

FIG. 7. Evoked afterdischarge in the orbital cortex of schizophrenic patient (RE) and spontaneous seizure in the temporal lobe of epileptic patient (OC) did not influence the EKG. However, evoked afterdischarges localized in few contacts of the temporal lobe in epileptic patient (HL) modified the EKG rhythm.

of the cat invariably depress the blood pressure, but hypertension resulted when the seizure propagated to the hippocampus and fornix.

Some contradictions existed in our experiments. Stimulation of some points of the motor cortex in the cat modified blood pressure and heart rate, but similar stimulations in the monkey did not alter the EKG, even if motor afterdischarges were produced. In the cat, convulsive activity in the substantia nigra did not affect blood pressure or heart rate, but its electrical stimulation in the monkey did. Specie differences could be involved, but another possible explanation might be the difficulty common to all experiments of cerebral stimulation, namely, to identify the structure which is responsible for the observed effect. Usually several structures are close to each electrical contact, and in addition to this proximity, the relative excitability of each structure is an important factor. Also, as we have seen in previous studies (4), stimulation of one cerebral point may activate areas located many millimeters distant.

The existence of generalized seizure activity without cardiovascular effects surprised us, and no clear explanation can be offered. We might speculate that cerebral structures of antagonistic functions were simultaneously activated, cancelling effects, or that the afterdischarges blocked pathways involved in some of the cardiovascular reactions. A similar problem was to explain why consciousness was unimpaired in some patients with generalized afterdischarges, but was affected in cases with localized seizure activity. The important factor does not seem to be the extent of brain involved, but rather the pattern of the discharge and the areas of the brain affected (3).

The controversy concerning the presence of seizure activity as essential (12) or dispensable (7) for the production of pressor responses may be resolved by accepting both cases as possible, depending on which structure is being considered. In the majority of our experiments increases of blood pressure and cardiac arrhythmia were evoked without producing any disturbance in the electrical activity of the brain. In a few points, however, (orbital cortex of the cat, for example), the existence of the afterdischarge was essential to obtain pressor responses. In this last case several explanations were possible: pressor effects could have high threshold; or a local afterdischarge could be necessary to activate neurons with autonomic function; or the seizure could spread to other cerebral areas which were responsible for the cardiovascular responses.

Motor activity was not necessarily related to pressure and cardiac manifestations because they could be evoked independently of each other. Pool and Ransohoff (14) have described a persistence of pressor effects in humans for as long as five minutes after stimulation of the rostral part of the cingulate gyrus. Our experiments showed that in the monkey the EKG disturbances lasted more than one minute after only 5 seconds of stimulation in the absence of any observable EEG or behavioral reaction. The possible role of central and peripheral factors in the persistence of this effect is a very interesting problem, which deserves further investigation.

SUMMARY

Cerebro - cardiovascular relations have been studied in unanesthetized cats, monkeys and humans, with electrodes implanted in the brain. Blood pressure was recorded in free-moving cats with the aid of permanent intraarterial cannulas and a transducer carried by the animal. Results were as follows.

Electrical stimulation of some points of the motor cortex (cat) subiculum, posterior hippocampus and substantia nigra (monkey) produced cardiovascular effects, with-

out any alteration in the spontaneous electrical activity of the brain.

Electrical stimulation of the orbital cortex (cat), central gray, fornix (monkey) and temporal lobe (human) produced cardiovascular effects only if intensities strong enough to evoke afterdischarges were used.

Afterdischarges localized in the the thalamus, substantia nigra (cat), motor cortex, amygdala, thalamus (monkey), orbital cortex (human) were not accompanied by cardiovascular manifestations.

The above-mentioned results show that cardiovascular effects may be evoked without disturbance of the electric activity of the brain, and seizure activity may exist in the absence of cardiovascular reactions—proving the independence of both phenomena.

Specificity of cardiovascular representation in the brain was demonstrated by the fact that electrical stimulation of different structures modified selectively the heart rate, evoked ectopic atrial beats, altered the blood pressure or produced ventricular extrasystoles with patterns typical for different cerebral areas.

REFERENCES

1. Andy, O. J., Bonn, P., Chinn, R. M., and Allen, M. Blood pressure alterations secondary to amygdaloid and periamygdaloid afterdischarges. J. Neurophysiol., **22**: 51–60, 1959.
2. Delgado, J. M. R. Evaluation of permanent implantation of electrodes within the brain. Electroencephalog. & Clin. Neurophysiol., **7**: 637–644, 1955.
3. Delgado, J. M. R. and Hamlin, H. Direct recording of spontaneous and evoked seizures in epileptics. Electroencephalog. & Clin. Neurophysiol., **10**: 463–486, 1958.
4. Delgado, J. M. R. and Hamlin, H. Spontaneous and evoked electrical seizures in animals and human. Conference on electrical studies on the unanesthetized brain. Georgetown Univ. Medical School. To be published.
5. Folkow, B. Nervous control of the blood vessels. Physiol. Rev., **35**: 629–663, 1955.
6. Hess, W. R. *Beiträge zur Physiologie des Hirnstammes. I. Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnabschnitte*. Thieme, Leipzig, 1932.
7. Hoff, E. C. and Green, H. D. Cardiovascular reactions induced by electrical stimulation of the cerebral cortex. Am. J. Physiol., **117**: 411–422, 1936.
8. Janjigian, E. Cardiac epilepsy simulating anginal syndrome. EEG clin. Neurophysiol. **3**: 103, 1951.
9. Kaada, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of 'rhinencephalic' and other structures in primates, cat and dog. Acta physiol. scandinav., **24**: supp. 83, 1951.
10. McDowall, R. J. S. *The Control of the Circulation of the Blood*. Dawson, London, 1956.
11. Mihailović, Lj., Antić, R., Vasiljević, D., and Krzalić, Lj. The effects of Thialbarbitone (Kemithal) on the myocardium. Acta med. iugosl. *13:* 32–55, 1959.
12. Morin, G., Corriol, J. and Zwirn, P. Signification de l'hypertension artérielle provoquée par la stimulation électriqu du gyrus simoide. J. Physiol., **45**: 202–203, 1953.
13. Phizackerley, P. J. R., Poole, E. W., and Whitty, C. W. M. Sino-auricular heart block as an epileptic manifestation. Epilepsia (Boston) **3**: 89–91, 1954.
14. Pool, J. L. and Ransohoff, J. Autonomic effects on stimulating rostral portion of cingulate gyri in man. J. Neurophysiol., **12**: 385–392, 1949.
15. Rushmer, R. F. and Smith, O. A., Jr. Cardiac control. Physiol. Rev., **39**: 41–68, 1959.
16. Spiegel, E. A. and Hunsicker, W. C., Jr. The conduction of cortical impulses to the autonomic system. J. Nerv. & Ment. Dis., **83**: 252–274, 1936.

POSITIONAL NYSTAGMUS IN MAN AND ANIMALS[1]

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Since Bárány (4) described the positional nystagmus a substantial progress has been made in disclosing its etiology, varieties and clinical importance. Standardization of positional test and nystagmographic recording are outstanding advances of modern otoneurology. Unfortunately, there have been no serious attempts to establish an agreement regarding its nomenclature and classification. In contrast to the clinical progress, the understanding of neural mechanisms underlying the release of positional nystagmus remains an obscure subject.

This report presents a brief account of some clinical and experimental observations which may have a bearing on these matters.

OBSERVATION ON NOMENCLATURE AND CLASSIFICATION

Several classifications of positional nystagmus have been proposed. They are known by the author's name, which always should be specified to avoid confusion. The proposals of Nylén (21–23), Seiferth (25), Lindsay (18), Frenzel (12), Aubry *et al.* (3) and Aschan *et al.* (2) are often used in the literature.

The nomenclature and classification of Nylén (23) has been accepted by most authors. The criteria of Nylén and other observers for labelling the positional nystagmus is based on its direction and duration. If the direction changes in certain positions of the head then the nystagmus is called "direction-changing" and is classified as Type I. If the direction does not change, then it is called "direction-fixed" and classified as Type II. If the nystagmus varies from one test to another, *i.e.* sometimes is direction-changing, sometimes direction-fixed or during the same head position changes its direction, then is called "irregular" and classified as Type III. If the positional nystagmus (Types I, II, and III) persists as long as the position of the head is maintained, it is called "tonic" and if it lasts for a limited time, it is called "transitory." Aschan *et al.* (2) proposed to change the term "tonic" to "persistent." This change in Nylén's classification seems to be justified, because the new term describes more objectively its presence for unlimited time.

Aschan *et al.* (2) proposed a fundamental change in Nylén's classification, as follows. Type I includes only the "persistent direction-changing"; Type II, the "persistent direction-fixed"; and Type III all varieties of "transitory" positional nystagmus, such as the transitory of Nylen, irregular, transitional, paroxysmal, etc. The advantage of this classification is that Types I and II are not only perfectly defined, but may have a different clinical value than Type III. The "persistent" types often are associated with central nervous system diseases, while diseases of benign cause often are associated with "transitory" forms. According to Aschan *et al.* the "persistent" types call for a thorough neurologic examination.

The inclusion of all varieties of transitory positional nystagmus in Type III may be a weak point in this classification. The objection is that from the physiopathologic point of view these varieties may not be related to the same change in the neural mechanism. It is probable that a better understanding of this mechanism would lead to a more accurate interpretation of the transitory forms.

A weak point in the nomenclature of po-

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sitional nystagmus is its definition in terms of duration as "persistent" and "transitory." Clinical observations reveal that the distinction between the one and the other provides significant diagnostic information, but on theoretical grounds the distinction is questionable. The transitory type is by definition any positional nystagmus which lasts for a limited time. This time has been fixed by Dix and Hallpike (9) and Aschan *et al.* (2) at 20 seconds, Frenzel (12) at 30 seconds and Lindsay (18) at 60 seconds. Obviously these limits represent the personal experience and judgment of the observers. The objection to these opinions is that a postural nystagmus lasting, let us say, two, five or ten minutes is also transitory. Whether the sharp limit as given by the previous authors is significant, remains to be investigated. The term "persistent," on the other hand, may be interpreted as indicating that the positional nystagmus is present as long as the position is maintained. Since in practice positional nystagmus is observed for a few minutes at most, the question remains whether all or some so-called "persistent" types may become extinct when the position is maintained for sufficient time. For this reason the term "persistent" only indicates that the positional nystagmus was seen for a reasonable time and that the end-point is not known.

Among the transitory forms, the "benign paroxysmal" type as described by Dix and Hallpike (9) and Citron and Hallpike (8) has been associated with diseases of benign nature. The term "benign" however has been questioned by some investigators because it may be interpreted as always indicating a mild lesion. The objection was raised by Riesco (24) after describing a "benign paroxysmal" type of postural nystagmus in a case of astrocytome of the posterior vermis of the cerebellum. The opinion of Riesco has been supported by experimental observations of Allen and Fernández (1) and Fernández *et al.* (10, 11). They reported that in the cat, a "benign paroxysmal" type of postural nystagmus may follow a lesion of the cerebellum which includes the nodulus. On the other hand, the term "paroxysmal" is an important addition in the nomenclature of positional nystagmus. It defines a nystagmus with striking characteristics which cannot be confused with other transitory forms.

The line of division between transitory and persistent types as defined in the clinic, cannot be applied to experimental animals. In the cat the borderline was found to be three minutes by observations following cerebellar damage (1, 11) or certain localized labyrinthine lesions (10). This finding was clear-cut, but experiments still in progress suggest that if the change in position is maintained for several hours, then the so-called "persistent" positional nystagmus tends to disappear. Whether a human being with a persistent positional nystagmus will habituate, as does the cat, is not known.

The positional nystagmus of experimental animals may differ from that of man in several characteristics. For instance, ablation of the nodulus in the cat (11) was usually followed by a direction-fixed positional nystagmus toward lower eyelids. In some animals it was transitory, in other persistent. Both transitory and persistent types compensated in about ten days. The persistent always changed with time into transitory with paroxysmal characteristics or transitory with one or several paroxysmal spells, as Figure 1 illustrates. These spells may escape direct observation. Cerebellar lesions in men may be accompanied by positional nystagmus of any variety. Compensation, if it ever occurs, is a process which may take place in months or years. As far as we know, paroxysmal spells superimposed upon a transitory or persistent positional nystagmus, have not been described in man. This probably is due to difficulty in detecting it by direct observation.

Peripheral lesions in experimental animals also may be followed by positional nystagmus which differs from that seen in

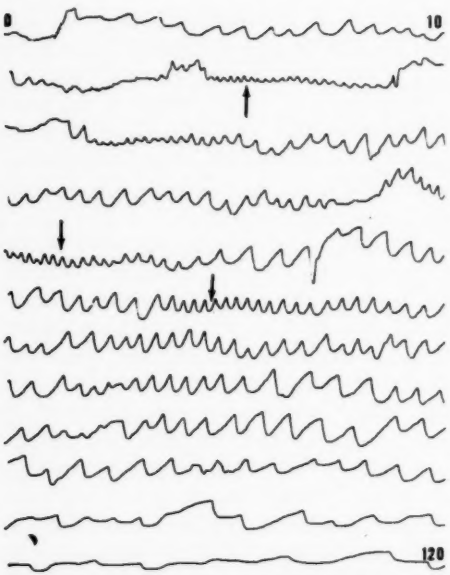

FIG. 1. Cat A-674. Nystagmograph taken in supine position two days after ablation of the nodulus. The positional nystagmus was the direction-fixed type beating toward lower eyelids. It lasted 120 seconds. Notice the recurrence of nystagmic outbursts as arrows indicate. In this and following nystagmographs, the electrodes were placed in a vertical plane and the direction of the nystagmus was always toward lower eyelids. The graphs represent a continuous recording, reading from left to right; numerals indicate time in seconds and the instant the animal was rotated from a standing position to a new position is signified by a zero mark. This and following figures were taken from Fernandez *et al.*, Ann. Otol. Rhin. & Laryng., in press.

man with labyrinthine diseases. Rapid compensation is the most prominent feature in animals and often spontaneous nystagmus for a few hours preceded the appearance of positional nystagmus (10, 16). These findings correspond in certain particulars to the observation which is characteristic of certain types of labyrinthine disturbance in the human. For example, in the acute labyrinthine disturbance which frequently follows a severe head blow, the patient may have a spontaneous nystagmus at the onset within a variable period; for perhaps one to several days the nystagmus is no longer continuous but reappears only when certain positions are assumed.

The latency of positional nystagmus is a matter which has not been considered in the classifications already mentioned. This is probably due to the fact that its clinical importance still remains a subject of much controversy. Experience with human material shows that the "persistent" type of nystagmus usually appears without latency, although latency may be observed in some transitory forms. According to Dix and Hallpike (9) onset of the "benign paroxysmal" type is characterized by a latency of six seconds or less. However, it is a common observation to see patients in which the onset of a "paroxysmal" nystagmus appears during the movement from one position to another. This is often observed during the change from a supine to an erect position. The fact that the onset appears during movement does not mean necessarily that it was provoked by the movement itself. So far, no attempt has been made to explain the mechanism underlying the latency of positional nystagmus.

In animals latency was observed in both the persistent and transitory types (11). Figure 2 shows a paroxysmal nystagmus with a latency of 38 seconds. A long latency was seen more often in animals with a strong reaction to the positional test. This reaction was manifested by an episode of vocalization, struggling and occasionally urination. These signs of stress may appear during the turning of the animal and sometimes after a change in position has taken place. In either case the positional nystagmus was inhibited, for more or less time, depending upon the strength of the signs of discomfort. Our experiences obtained from a long series of animals enabled us to predict episodes of stress; sudden interruption of the nystagmus, state of alertness of the animal and a twitching of the head, all preceded by a few seconds the appearance of vocalization and/or struggling. These ob-

servations suggested strongly that the vestibular responses can be modified by some central neural mechanism. Whether this is accomplished through a descending system and whether it acts upon vestibular centers and/or receptors is not known. An open question is whether the latency of positional nystagmus is a phenomenon related to inhibition (peripheral or central) brought about by some efferent system.

An example of latency in a persistent positional nystagmus is illustrated in Figure 3. This is one of the animals which presented no episodes of stress. Similarly, an example of latency of a transitory type in an animal which presented no stress is shown in Figure 4. This nystagmograph was taken in hanging head position. In supine position the same type of positional nystagmus, that is, paroxysmal bouts superimposed on a transitory type, were present but had no latency (see Figure 1). Although this difference was reproducible, the relation between latency and certain positions is not clear.

Difference in species and experimental conditions are factors which may account for dissimilarities in vestibular disorders as seen in man and animals.

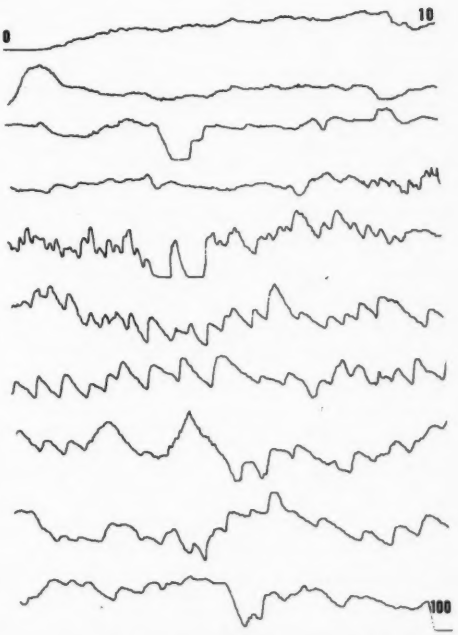

FIG. 2. Cat A-660. Nystagmograph taken in supine position three days after ablation of the nodulus, illustrating a latency of 38 seconds in a paroxysmal positional nystagmus.

OBSERVATIONS ON CLINICAL IMPORTANCE

All observers recognize that a careful assessment of positional nystagmus and its relation to the presence or absence of other symptoms may determine whether the vestibular disorder is peripheral or central. There is no variety of positional nystagmus which *per se* may be evaluated with certainty as a sign of localization. All types of positional nystagmus have been described in both peripheral and central vestibular affections; however, the former release predominantly transitory types while the latter are associated more frequently with persistent types. Both transitory and persistent types have been described in conditions of uncertain localization, such as drugs, infection and vascular disorders.

Nylén (21–23) Dix and Hallpike (9), Lindsay (17, 18), Aschan *et al.* (2) and others, have pointed out that the characteristics of positional nystagmus have a prognostic value. In general, the transitory forms are associated with benign lesions, while in the persistent forms, the prognosis is uncertain until a thorough neurologic examination may disclose the cause.

A point of much controversy is whether positional nystagmus of peripheral origin is produced exclusively by disorders of the otolithic apparatus. Dix and Hallpike (9) and other writers (6–14) have maintained that the "benign paroxysmal" type is due to a qualitatively abnormal response of the otolithic apparatus. On the other hand, Lindsay and Hemenway (19) have pro-

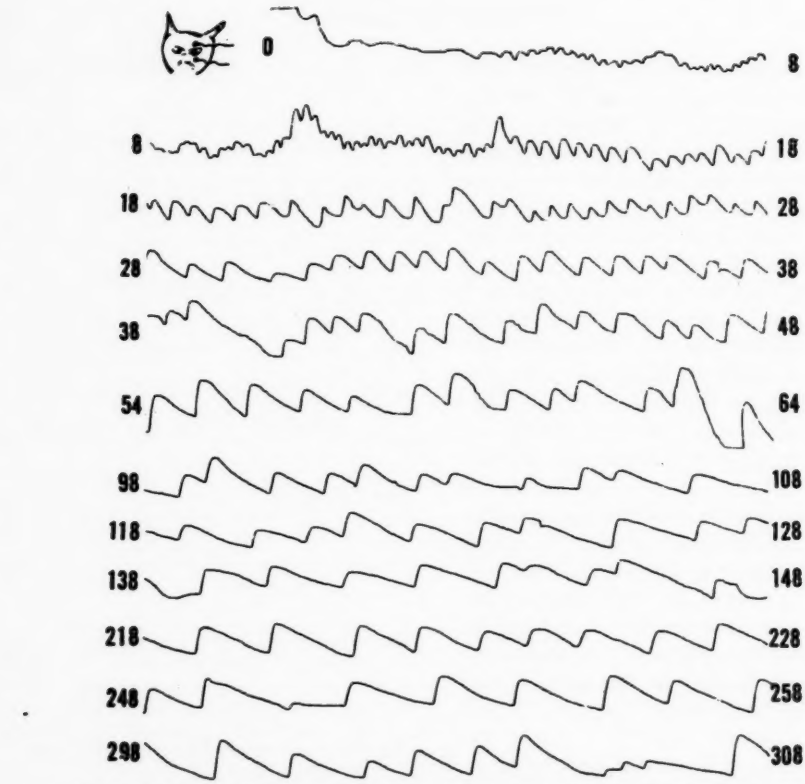

FIG. 3. Cat A-596. Nystagmograph taken in hanging head position three days after ablation of the nodulus. The figure is composed of twelve samples taken during the first five minutes and illustrates a case of latency of a persistent type of positional nystagmus.

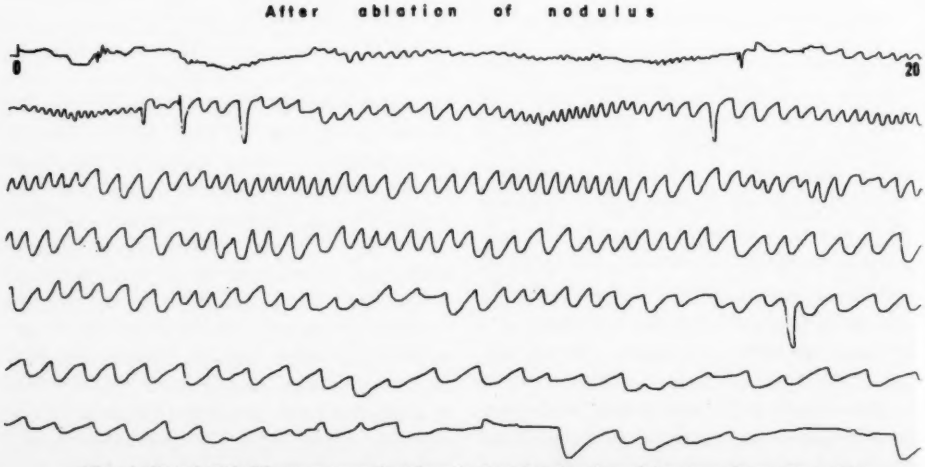

FIG. 4. Cat A-674. Nystagmograph taken in hanging head position two days after ablation of the nodulus. The onset of nystagmus was delayed and nystagmic outbursts occurred from time to time. In supine position no latency was present although other characteristics of the nystagmus were similar. Compare with tracings of Figure 1.

posed that positional nystagmus of peripheral origin including the "benign paroxysmal" type is due to an asymmetric response of the two vestibular sense organs. The asymmetry takes place only when the lesion is unilateral, sudden and partial. Total loss or slowly developing partial damage are not followed by positional nystagmus. The vestibular disorder may be originated by a lesion or disturbance in any receptor or combination of receptors, provided the conditions already mentioned are fulfilled. Positional nystagmus may also be associated with damage of the primary afferent neurons (19). The opinion of Lindsay and Hemenway (19) has been supported by experimental observations in the cat (10). In this investigation it was found that positional nystagmus followed a section of either utricular or lateral ampullary nerves, or a combined section of both plus the superior ampullary nerve. Unilateral labyrinthectomy produced only spontaneous nystagmus. It was demonstrated also that conjugate movements of the eyes but no nystagmus was associated with electric stimulation of the utricular nerve. These findings in conjunction with other observations (15, 20) are important, because they strongly suggest that positional nystagmus of peripheral origin is not necessarily produced by disturbances of the otolithic apparatus.

OBSERVATIONS ON PHYSIOPATHOLOGY

All attempts to explain the neural mechanism underlying the release of positional nystagmus, peripheral or central, are impeded by incomplete information of the neuroanatomy and physiology of the vestibular system. Even in cases of known lesions in the vestibulo-ocular pathways, the explanation is based on assumptions. In case the lesion does not involve these pathways, for instance, tumors of anterior fossa or cerebellar damage the explanation is still more obscure. However, there are a few experimental observations indicating that release of the vestibular centers from cerebellar inhibition may be accompanied by positional nystagmus. Spiegel and Scala (26, 27) demonstrated in the cat that positional nystagmus was associated with a lesion of posterior vermis which did not involve the medullary centers. Further observations of Allen and Fernández (1) and Fernández *et al.* (11) established that the vestibular disorder appeared when the cerebellar lesion involved the nodulus. These and other findings (5) are important from the physiological and clinical point of view. Physiologically, they indicate that there is a functional localization of the vestibular system in the nodulus. So far, the nodulus seems to have a triple function. It acts as 1) an inhibitor of vestibulo-ocular reflex arc (11, 22, 23); 2) facilitator of vestibulovegetative reflexes (5); and 3) maintainer of equilibratory reflexes independently of the peripheral vestibular, other proprioceptive and the ocular systems (11). Clinically, the importance of these experimental observations is that the positional nystagmus and disturbances of equilibrium associated with lesions of posterior fossa do not necessarily mean involvement of vestibulo-ocular and/or vestibulo-spinal pathways.

The experiments already mentioned (1, 11, 22, 23) also demonstrate an important point for the understanding of the neural mechanism of positional nystagmus following lesions of the cerebellar vermis. That is, the presence of signals from peripheral receptors indicating change in position are necessary for releasing this positional nystagmus. In the cat, positional nystagmus following lesions of the nodulus is eliminated after bilateral labyrinthectomy, and conversely, it cannot be elicited if bilateral labyrinthectomy precedes the lesion. The question whether positional nystagmus can be elicited by some other means after bilateral labyrinthectomy (13) still remains to be answered.

SUMMARY

The definition of positional nystagmus in terms of transitory and persistent is a weak point in most classifications. In practice the distinction between one and the other provides significant diagnostic information but on theoretical grounds the distinction is questionable. Since in practice positional nystagmus is observed for a few minutes at most, the question remains whether all or some so-called persistent types may disappear when position is maintained for sufficient time.

The benign paroxysmal type of positional nystagmus is usually associated with diseases of mild course. There are objections to the term "benign," however, because this type of positional nystagmus has been observed in both man and animals with cerebellar lesions.

Positional nystagmus following both labyrinthine and cerebellar lesions in animals differs from that seen in man with similar diseases. One of the most striking differences is that animals compensate rapidly after either peripheral or central damage.

Persistent types of positional nystagmus in man usually present no latency, while in animals latency may be observed. The transitory types, such as the "paroxysmal" in both man and animals, may or may not present latency.

Clinical and experimental evidence suggest strongly that positional nystagmus of peripheral origin is not necessarily produced by disturbance of the otolithic apparatus.

Experimental observations indicate that the nodulus of the cerebellum has a triple function: inhibition of the vestibulo-ocular reflex arc, facilitation of the vestibulo-vegetative reflexes, and maintenance of equilibrium independently of the peripheral vestibular, other proprioceptors and the ocular systems.

Experimental ablation of the nodulus in the cat suggests that positional nystagmus and disequilibrium do not necessarily mean involvement of the vestibulo-ocular and/or vestibulo-spinal pathways.

The presence of signals from peripheral receptors indicating change in position are necessary for releasing the positional nystagmus due to lesions of the cerebellar vermis in the cat.

REFERENCES

1. Allen, G. and Fernández, C. Experimental observations on postural nystagmus. I. Extensive lesions of the cerebellum. Acta. oto-laryng. In press.
2. Aschan, G., Bergstedt, M. and Stahle, J. Nystagmography. Recording of nystagmus in clinical neuro-otological examination. Acta oto-laryng., supp. 129, 1956.
3. Aubry, M., Pialoux, P. and Bouchet, J. Le nystagmus de position en oto-neurologie. Ann. oto-laryng., **71**: 531–559, 1954.
4. Bárány, R. Diagnose von Krankeitserscheinungen im Bereiche des Oto-lithenapparates. Acta oto-laryng., **2**: 434–437, 1921.
5. Bard, P., Woolsey, C. N., Snider, R. S., Mountcastle, V. B. and Bromiley, R. B. Delimitation of central nervous mechanisms involved in motion sickness. Fed. Proc., **6**: 72, 1947.
6. Carmichael, E. A., Dix, M. R. and Hallpike, C. S. Pathology, symptomatology and diagnosis of organic affections of the eighth nerve system. Brit. M. Bull., **12**: 146–152, 1956.
7. Cawthorne, T. E., Dix, M. R., Hallpike, C. S. and Hood, J. D. The investigation of vestibular function. Brit. M. Bull., **12**: 131–142, 1956.
8. Citron, L. and Hallpike, C. S. Observations upon the mechanism of positional nystagmus of the so-called "benign paroxysmal type". J. Laryng. & Otol., **70**: 253–259, 1956.
9. Dix, M. R. and Hallpike, C. S. The pathology, symptomatology and diagnosis of certain common disorders of the vestibular system. Ann. Otol. Rhin. & Laryng., **61**: 1007–1016, 1952.
10. Fernández, C., Alzate, R. and Lindsay, J. R. Experimental observations on postural nystagmus in the cat. Ann. Otol. Rhin. & Laryng., **68**: 816–830, 1959.
11. Fernández, C., Alzate, R. and Lindsay, J. R. Experimental observations on postural nystagmus. II. Lesions in the nodulus. Ann. Otol. Rhin. & Laryng. In press.
12. Frenzel, H. *Spontan-und Provokations-nystagmus als Krankheitssymptom: Ein Leitfaden für seine Beobachtung, Aufzeichnung und Formanalyse*. Springer, Berlin, 1954.
13. Fromm, B. and Nylén, C. O. Contribution to symptomatology of transplanted brain tumors in rats with and without labyrinths. Acta oto-laryng., **23**: 1–49, 1935.
14. Gerlings, P. G. Peripheral positional nystagmus. J. Laryng. & Otol., **62**: 147–162, 1948.

15. Graybiel, A., Niven, J. I. and Walsh, T. E. The differentiation between symptoms referable to the otolith organ and semicircular canals in patients with non-suppurative labyrinthitis. U.S. Naval School Aviat. Med. Proj. No. NM-001 059.01.29, 1952.
16. Hennebert, D. and Fernández, C. Ototoxicity of quinine in experimental animals. A.M.A. Arch. Otolaryng., **70**: 321–333, 1959.
17. Lindsay, J. R. The significance of positional nystagmus in otoneurological diagnosis. Laryngoscope, 55: 527–551, 1945.
18. Lindsay, J. R. Postural vertigo and positional nystagmus. Ann. Otol. Rhin. & Laryng., **60**: 1134–1150, 1951.
19. Lindsay, J. R. and Hemenway, W. G. Postural vertigo due to unilateral sudden partial loss of vestibular function. Ann. Otol. Rhin. & Laryng., **65**: 692–706, 1956.
20. Maxwell, S. S. Labyrinth and equilibrium. II. The mechanism of the static functions of the labyrinth. J. Gen. Physiol., **2**: 157–162, 1920.
21. Nylén, C. O. A clinical study on positional nystagmus in cases of brain tumors. Acta oto-laryng., supp. 15, 1931.
22. Nylén, C. O. The oto-neurological diagnosis of tumors of the brain. Acta oto-laryng., supp. 33, 1939.
23. Nylén, C. O. Positional nystagmus. A review and future prospects. J. Laryng. & Otol., **64**: 295–318, 1950.
24. Riesco Mac-Clure, J. S. Es el vértigo aural de origen exclusivamente periférico. Rev. otorrinolaring., **17**: 42–54, 1957.
25. Seiferth, L. B. Die Bedeutung des Lagenystagmus für die otologische und neurologische Diagnostik. Arch. f. Ohren-, Nasen-u. Kehlkopfh., **143**: 52–74, 1937.
26. Spiegel, E. A. and Scala, N. P. Vertical nystagmus following lesions of the cerebellar vermis. Arch. Ophth., **26**: 661–669, 1941.
27. Spiegel, E. A. and Scala, N. P. Positional nystagmus in cerebellar lesions. J. Neurophysiol., **5**: 247–260, 1942.

SECONDARY MICROTELEOPSIA IN UNILATERAL DISEQUILIBRIUM

L. HALPERN, M.D.[1] AND S. KUGELMASS, PH.D.[1]

It is known that sensory functions are altered when the underlying structures undergo pathological changes. Studies of unilateral disequilibrium involving sensorimotor induction reveal that, apart from direct changes in sensory functions, there also occur indirect sensory disturbances. These indirect sensory changes are induced and systematically influenced by the unilaterally disturbed body posture, and appear to be phenomenologically and physiopathologically of a special nature. The alterations thus induced occur principally on that side of the body which corresponds to the side of the disequilibrium. These disturbances usually consist on the one hand of a primary perceptual displacement of the coordinates in the visual, tactile and haptic spheres, and on the other hand of a dedifferentiation of the sensory perception and of quantitative perceptual changes. The quantitative changes of perception manifest themselves by a homolateral macrostereognosia or microstereognosia in the tactile sphere, and by a unilateral macropsia or micropsia in the visual sphere, both appearing on the side of the disequilibrium. The observations reported below refer to two patients presenting the sensorimotor induction syndrome in whom a homolateral secondary microteleopsia was encountered.

CLINICAL OBSERVATIONS

Case 1: General observations.

J.Z., a Frenchborn male aged 42, immigrated to Israel several years ago. At first he worked as an instructor in a new settlement, and then became manager of a cooperative general store. In September, 1954, in the course of a quarrel, he received a blow on the head and fell unconscious. In November of the same year he was again assaulted and lost consciousness. Following this episode he complained of attacks of pain in the left occiput, and of uncertainty when walking. After a short period of fever of unknown origin his pains increased, and were accompanied by a troublesome ringing in the left ear. He tried to continue his work, but on several occasions fell unconscious. During his first admission to the department four years ago the patient complained of dizziness, which increased when looking upwards and sidewards, and of clumsiness of his left extremities. The clinical examination revealed free movement of the eyes, normal reaction of the pupils, and normal fundi in both eyes. In the left eye, however, in contrast to the normal right eye, a concentric constriction of the field of vision was found. The limits of the constriction along the horizontal axis were 50′ temporal and 35′ nasal, and along the vertical axis 20′ above and 35′ below. The visus obtained on sciascopic examination was O.D. + 2.0 − Cyl + 1.0 Axis 135 5/9; O.S. + 3.50 − Cyl 3.0 Axis 45 5/60. The otological examination revealed a total deafness of the left ear, and nerve deafness, particularly for high tones, in the right ear. The caloric examination showed a total lack of reaction of the left labyrinth, while caloric reaction in the right ear was normal. All reflexes were normal. X-rays of the skull, the ears and the petrous tips were normal. The electroencephalogram showed an abnormal constant and diffuse theta activity of a frequency of 4c/s. The clinical picture was basically that of a left-sided sensorimotor induction syndrome in unilateral disequilibrium which will be detailed below.

The manifestation of teleomicropsia in unilateral disequilibrium.

In this patient the head trauma apparently caused a permanent impairment of the cochlear and vestibular functions on the left side, as well as a left-sided systematic disturbance of the equilibrium. The disturbance consisted of descent and deviation of the left arm and leg outwards to the left, of past-pointing the midline of the body with the left hand outwards to the left, of inclination of the body to the left when standing, and of

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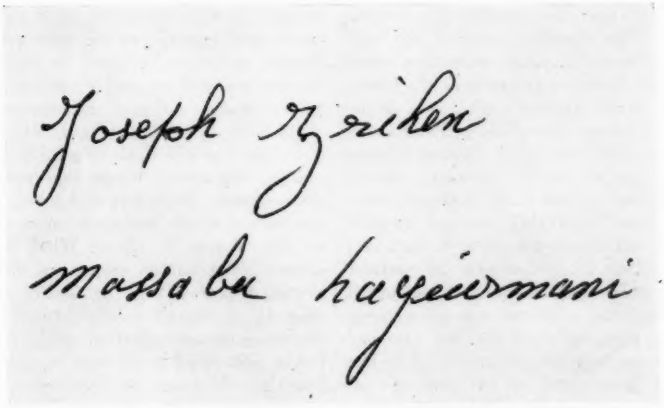

FIG. 1. Signature of patient J.Z. with only right eye open.

deviation to the left while walking with eyes closed. This displacement type of unilateral disturbance of the body posture had the features of the sensorimotor induction syndrome in that the basic tendency of displacement also expressed itself perceptually. The perceptual displacement was noted during the patient's attempt to localize a rod in space. When requested to place a rod in a vertical position with both eyes closed, he held it with its lower end inclined to the left. Similarly, when asked to hold a rod in a horizontal position he placed it with its left end downwards. Since the haptic localization, after all, involves motor management, the perceptual displacement tendency became even more apparent in the passive visual perception of the horizontal and the vertical. While using only the right eye the patient perceived the spatial coordinates correctly. When he used the left eye, however, a displacement of the spatial coordinates appeared as in haptic localization. An objective vertical seemed to him to be inclined about 15′ to the left, while the objective horizontal seemed to be inclined about 10′ down to the left. Some of the secondary disturbances of perception usually accompanying this primary displacement defect were also found in this case. These consisted of an induced diminution of superficial and deep sensibility on the left side, and an underestimation of size or microstereognosia in the left hand. In addition a left-sided teleomicropsia was found. The patient perceived distances normally with his right eye. When he used his left only, however, the object seen at first in its normal size, seemed to become more distant and increasingly small. The subjective distance was generally about double that of the objective distance. The physician, the nurse, a picture or any other object placed before the patient at a distance of two metres seemed, when looked at with the left eye, to be approximately four metres away. As the fixated object appeared to diminish, its contours became blurred. This phenomenon was observed consistently during the whole period of the patient's hospitalization. It might be mentioned that the patient did not complain of any particular disturbance of vision when using both eyes. His handwriting was also normal when using both eyes. When, however, he was asked to write with one eye open at a time, a striking difference in his handwriting was revealed. With only the right eye open, the patient wrote, as with both eyes open, in his normal and characteristic handwriting (Figure 1). During vision with only the left eye, however, the writing of the same text took on an unusual form (Figure 2). The text was squeezed together within a very small space, the single letters being so compressed

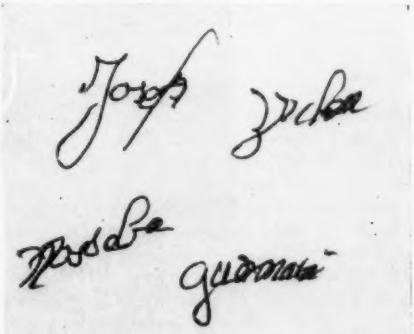

FIG. 2. Signature of patient J.Z. with only left eye open.

into one another that his handwriting became nearly illegible. This crowding occurred not only when the patient wrote his name, address or other text, but also when he was asked to write the letters of the alphabet. With only the right eye open the letters of the alphabet were clearly written and evenly spaced both in Latin and in Hebrew (Figure 3a). When only the left eye was open, the letters of both the Hebrew and the Latin alphabets were so crowded together that they became illegible (Figure 3b). An additional difference to be noted is in the angle of the line of writing. In contrast to the straight horizontal line of writing which was recorded while the right eye was open, there was a deviation upwards when the left eye was open. This deviation upwards occurred both in the Hebrew writing from right to left and in the Latin writing from left to right. The patient himself was not aware of these changes as long as he looked with his left eye, and noted it with surprise upon seeing this writing with his right eye.

Four years later the patient was readmitted to the department. The same basic features described above were also found during this hospitalization. New studies of his handwriting were carried out. Seated comfortably before a desk the patient was asked to write his name on a slip of paper 14 cm by 10 cm. After he finished that slip was removed and a similar one was placed before him with the request to write his name once more. These slips were always placed in the same position, perpendicular to him on the desk. In this manner a continuous series of successive signatures could be obtained under different experimental conditions. With both eyes open (Figure 4a), or when only the right eye was open (Figure 4b), no particular change was noted. When, however, only the left eye was open, there was an immediate crowding of the letters which increased successively from slip to slip (Figure 4c, d, e). When both eyes were opened there was an immediate return to normal writing (Figure 4f). In the light of previous experience which showed a color effect in patients with the sensorimotor induction syndrome, color stimulation was tried while the patient was writing. Placing a Wratten No. 47 blue filter before the contralateral eye, which up to now had been associated with normal handwriting, produced no change (Figure 5a). A striking effect, however, was produced by placing a Wratten No. 29 red filter before this eye. There was an immediate and successive crowding of the letters similar to that which had appeared spontaneously when the patient used the left eye (Figure 5b, c, d). Replacing the red filter by a blue one led to an immediate normalization of the handwriting (Figure 5e). In the course of the investigations the handwriting of the patient was also recorded when both eyes were

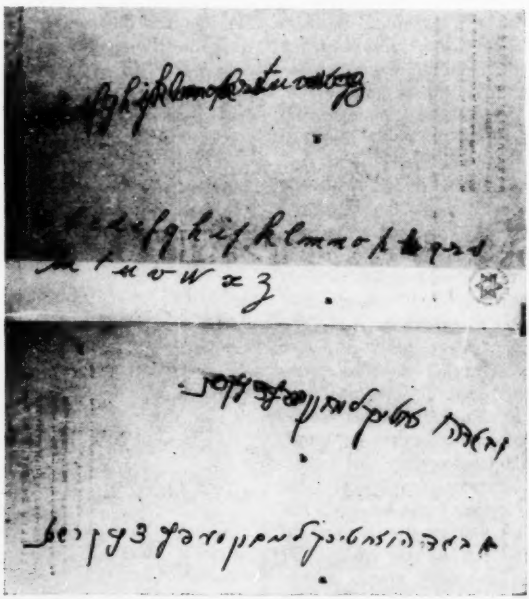

FIG. 3. Latin and Hebrew alphabets written by patient J.Z. a: with only the right eye open; b: with only the left eye open.

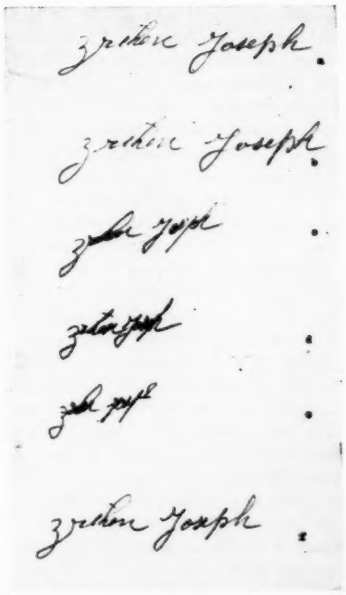

FIG. 4. Successive signatures of patient J.Z. a: with both eyes open; b: with only the right eye open; c, d and e: with only the left eye open; f: with both eyes open.

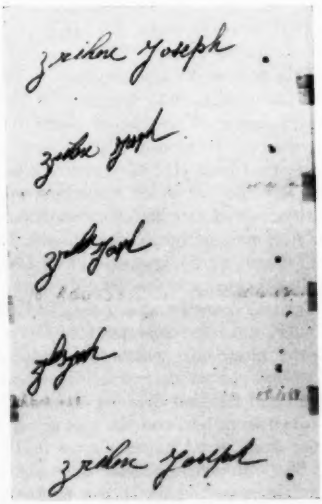

FIG. 5. Influence of colors on handwriting of patient J.Z. a: with Wratten No. 47 blue filter placed before the right eye; b, c and d: with Wratten No. 29 red filter placed before the right eye; e: with Wratten No. 47 blue filter placed before the right eye.

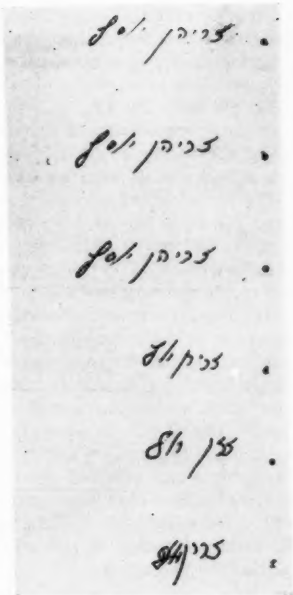

FIG. 6. Hebrew signatures of patient J.Z. a, b and c: with both eyes open, d, e and f: with both eyes closed.

closed. Under this condition, in contrast to the normal signatures with both eyes open (Figure 6a, b, c), the same typical abnormal handwriting appeared which had been noted when seeing with the left eye only, or when a red filter was placed before the right eye (Figure 6d, e, f). During the successive trials the letters became crowded progressively, with increasing distortion. It is to be noted that this is in sharp contrast to results obtained with normal individuals writing with eyes closed, where the handwriting is in general even more spread-out.

Case 2: General observations.

A.S., a woman aged 47, had undergone thyroidectomies at the ages of sixteen and twenty-four. During the last seven years she had suffered from transitory urinal retention, and sometimes from involuntary urination. For the past three years she noticed an unsteadiness when walking, which increased in the dark, and an inclination of her body to the left. The patient felt a clumsiness in her left extremities, and from time to time during the last year her vision became blurred.

On neurological examination pyramidal motility and reflexes, movements of the eyes, and reaction of the pupils and fundi were found to be normal.

The initial routine examination of the visual field showed normal boundaries in the left and right eye. The right field of vision remained unchanged during successive examinations, while the use of the same method with the left eye revealed progressive concentric constriction of the visual field. The limits of the resulting constriction were between 65′ temporal and 40′ nasal in the horizontal axis, and between 40′ above and 45′ below in the vertical axis. The visus was D 5/6 + 0.5 5/52; S 5/6 + 0.5 5/52. Audiometric examination showed normal bilateral hearing. The caloric examination showed very high sensitivity to the stimuli on both sides, and therefore a complete examination could not be carried out. Lumbar puncture revealed normal pressure with normal chemical and serological values. Normal results were also obtained in the X-ray of the skull, and in the routine electroencephalographic examination. A neurogenic bladder with fibromuscular hypertrophy of the internal sphincter was found and operated upon. In addition, in the foreground of the clinical picture, there existed a left-sided systematic disturbance of the equilibrium with symptoms of the sensorimotor induction to be described below.

The manifestation of teleomicropsia in unilateral disequilibrium.

Diagnostically it was assumed that this patient had suffered from disseminated sclerosis with a neurogenic bladder, and a left-sided impairment of equilibrium. This impairment of equilibrium manifested itself by a tendency to fall to the left when standing with her eyes closed, and by past-walking to the left. When the patient was asked to close her eyes and to extend her arms or to raise her legs while in a prone position, the left arm and leg descended and deviated outwards without the patient's being aware of it. The position of the extremities was systematically influenced by changes of head posture. Turning the head to the right had a corrective effect on the descent of the extremities, while turning the head to the left visibly increased and accelerated this descent. The unilaterally disturbed body posture, which was of the displacement type, induced a perceptual displacement of the coordinates of space in the visual sphere. She perceived a vertical and horizontal line accurately when using the right eye. When she looked with the left eye only, however, the vertical line seemed to be inclined with its upper end to the left, and the horizontal line appeared with its left end tilted downwards. There also existed secondary sensory disturbances, which, in addition to the above mentioned successive constriction of the left visual field, included an induced impairment of all qualities of superficial and deep sensibility of the whole left side of the body. Furthermore, during her estimation of equal objects in both hands, microstereognosia was found in the left hand. It became apparent that the spontaneous underestimation of the size of objects held by the left hand increased distinctly when the left eye alone was open. At the same time the phenomenon of microteleopsia was found to exist in the left eye. With the left eye open the patient consistently experienced that objects fixated by her appeared to be smaller and more distant. The nurse, for example, who stood at a distance of two metres from the patient, and who had appeared in her normal size when the patient was looking at her with her right eye, seemed to become smaller and smaller and to recede to a distance of six to seven metres when the left eye was used. Occasionally, and to a much lesser degree, the object was experienced to be smaller and more distant when the right eye alone was used. Placing a blue No. 47 Wratten filter before the left eye reduced the teleomicropic perception. Placing a red No. 29 Wratten filter before the left eye, however, had no influence on the existing disturbance, apart from evoking such an unpleasant feeling that the patient began to cry, and quickly removed the filter.

A series of recordings of the signatures of this patient was carried out while both her eyes were open, and during the opening of each eye alone. With both eyes open, or when only the right eye was open no particular deviations were noted (Figure 7a). However, when the left eye alone was open, an increasing upward tilt of the line of writing from the left to the right appeared (Figure 7b, c, d, e). The patient was unaware of this tendency, once running off the slip of paper. The same phenomenon may be seen in Figure 8a, b, c, where the placing of a blue No. 47 Wratten filter before the open left eye produced a striking correction in that the line of writing immediately returned to the almost normal horizontal (Figure 8d). The patient's teleomicropsia was also examined in the following way. She was seated at one end of a desk and given a pencil and a piece of blank paper 14 cm by 10 cm. She was aked to draw a two inch square filter box which was standing one metre away at the other end of the desk. When the patient had finished drawing the box, the paper was taken from her, and she was given another slip of the same sized paper placed in the same position. She was then requested to make another drawing of the same object. In this manner several series of drawings were obtained under different experimental conditions. The drawings obtained when the right eye alone was used did not reflect any particular tendency (Figure 9a, b, c, d). The drawings obtained when both eyes were open, however, indicate a gradual progressive reduction in

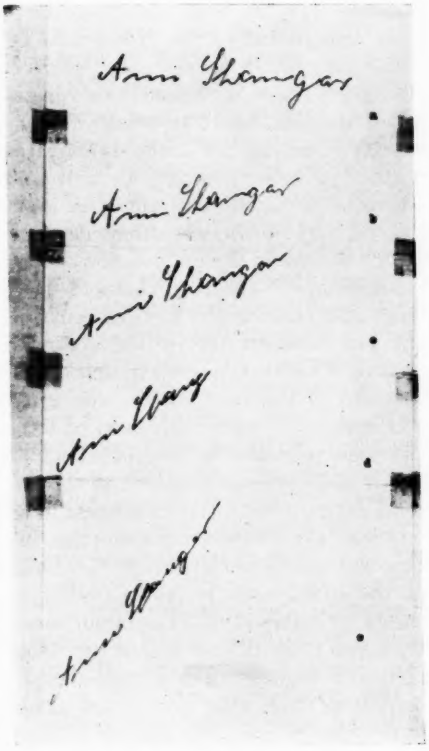

FIG. 7. Line of writing of patient A.S. a: with only the right eye open; b, c, d and e: with only the left eye open.

size (Figure 9e, f, g, h). This tendency toward reduction was much more evident when only the left eye was used, and was accompanied by a relative change in the dimensions drawn. The reduction along the horizontal dimension was striking compared with the reduction along the vertical axis (Figure 9i, j, k). In order to test the effect of blue on this phenomenon an additional series of signatures was obtained. Placing a blue No. 47 Wratten filter before the left eye clearly demonstrated a corrective influence (Figure 10h, i, j, and n).

Some of these examinations were repeated as long as a year and a half later, and essentially the same results were obtained.

COMMENT

Both patients suffered from a left-sided disequilibrium which in the first patient de-

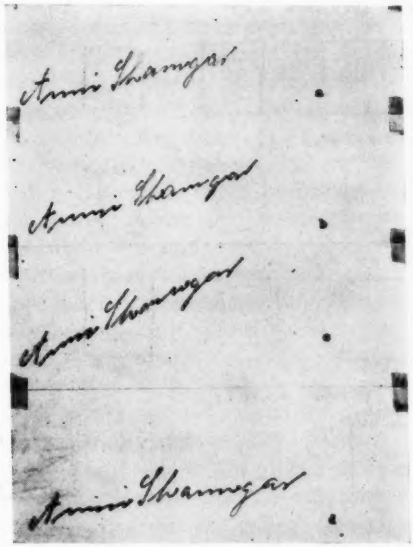

FIG. 8. The influence of blue on the line of writing of patient A.S. a, b and c: with the left eye only open; d: with Wratten No. 47 blue filter placed before the left eye.

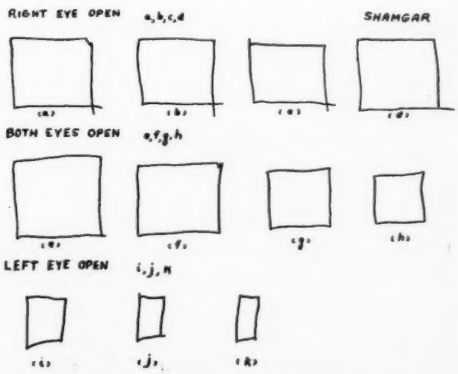

FIG. 9. Size changes in the tracings of original drawings by patient A.S. of filter box. a, b, c and d: when only the right eye was open; e, f, g and h: when both eyes were open; i, j and k: when only the left eye was open.

veloped after head trauma with resulting injury to the left cochleovestibular apparatus, and in the second patient probably appeared as part of disseminated sclerosis. As described above, the unilateral disequilibrium

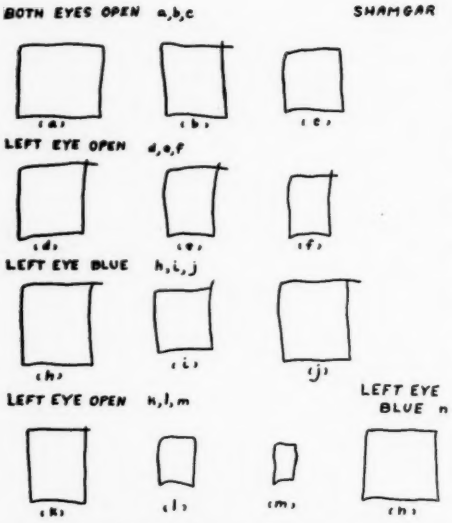

FIG. 10. Effect of blue on size and distortion of drawings by patient A.S. a, b and c: when both eyes were open; d, e and f: when left eye only was open; h, i and j: with blue filter before the left eye; k, l and m: when left eye only was open; n: replacement of blue filter before the left eye.

was accompanied in both patients by induced sensory disturbances, and had the features of the sensorimotor induction syndrome.

The primary sensorimotor symptoms of the syndrome observed in both patients include, in addition to the left sided postural displacement of the body as a whole and of the left extremities, a perceptual displacement of the vertical and horizontal coordinates in the ipsilateral left eye. The changed perception of horizontality also expressed itself in an upward deviation of the line of writing while both patients were using their left eye. In addition, this perceptual displacement appeared in the first patient during his following the request to place a rod in a vertical or horizontal position. Among the induced secondary disturbances is the above-mentioned concentric constriction of the left visual field which manifested itself in both patients in that eye which corresponds to the side of the disequilibrium. K. Goldstein (2), in 1933, described an induced constriction of the visual field in a similar patient. In severe cases, as in the first reported here, the homolateral constriction of the visual field is usually found to be present during the initial examination. In other patients, however, as in the second case, the constriction appeared gradually, as has previously been described, through the use of the method of successive examinations. The induced character of the visual field constriction in Goldstein's patient was demonstrated by the systematic influence of the head posture in that the displacement of the head to one side caused an improvement, while displacement to the other side provoked a deterioration. The induced and dynamic character of the ipsilateral constriction of the visual field in patients with the sensorimotor induction syndrome was also demonstrated by the finding that the constriction is systematically influenced by colors (10). Thus in our second case a red filter placed before the homolateral eye accelerated and increased the constriction, while this constriction gradually returned to normal under the influence of a blue filter. In both patients, in addition to this unilateral visual field constriction, there existed another disturbance involving a quantitative change in perception. This disturbance appeared in the tactile sphere in the form of a left handed microstereognosia, and in the visual sphere as a unilateral microteleopsia. This phenomenon presented itself once again ipsilaterally to the disequilibrium in the left eye.

Upon consideration of the character of the disturbances in the visual perception of size and distance, a distinction seems indicated between those of primary and secondary nature. Primary disturbances would include those caused by direct lesions of the visual pathways. Primary micropsia and macropsia are encountered, as is known, in retinal changes and also in central lesions where they are sometimes accompanied by teleopsia. Apart from their occasional ap-

pearance during the course of epileptic seizures they were encountered particularly in anatomically verified lesions of the visual tract. L. van Bogaert (12) described the phenomena of micropsia and teleopsia in a patient with homonymous hemianopsia in the right upper quadrant caused by a glioma of the left temporal lobe. M. Bender and N. Savitsky (1) reported on micropsia and teleopsia in a patient with bitemporal defects of the visual field due to an epidermoid tumor in the region of the chiasma.

The secondary micropsia and macropsia are, in contrast, indirectly induced dynamic phenomena which manifest themselves in spite of the anatomical integrity of the visual organ. These are found in patients with the sensorimotor induction syndrome, where they appear on the affected side. In these patients the perceptual change of size may affect not only the homolateral eye, but the homolateral tactile sense as well, in that the unilateral micropsia is accompanied by a homolateral microstereognosia. As mentioned above, there existed a left-sided microstereognosia in our patients too. Equally, when told to use each eye separately our patients were amazed to find that all objects which they had perceived normally while looking with the right eye, became smaller and appeared more distant when they used only the left eye. It is of interest that there was also a change in their handwriting and drawing of which they were not aware. Thus when the first patient was using his left eye, his handwriting was compressed into a narrow space, and when the second one used her left eye, there was a progressive reduction in the size of her drawings of a square. This size reduction was accompanied by a surprising distortion of form in that the horizontal sides of the square were proportionately more reduced than the vertical sides.

The induced character of the microteleopsia found in these patients was clearly demonstrated by the influence of colors. Placing a blue filter before the left eye had a corrective effect on the visual perception of size and distance as well as on their graphic representation. In the first patient, in whom the microteleopsia was more severe, the effect of blue seemed not to have been sufficient to have a corrective influence on the affected eye. The red filter, however, provoked the disturbance even when placed before the healthy contralateral right eye alone. The systematic effect of colors is a frequent feature of the sensorimotor induction syndrome in that blue corrects the existing disturbances while red aggravates them (4). The contrasting effect of these colors not only influences the statokinetic conditions and the various sensory disturbances induced by them, but also affects the general functioning of the organism (3). This was shown in studies on acoustic discomfort (6), vibratory perception (9), two-point discrimination (8), respiration and circulation (11), reaction time (7), and even states of consciousness (5). Homolateral microteleopsia in unilateral disequilibrium should thus be included among the secondary disturbances which may be influenced by colors.

The mechanism of the induced unilateral microteleopsia is difficult to clarify. Some connection between this disturbance and the homolateral constriction of the visual field might be assumed, insofar as both phenomena are influenced by colors, and as the impairment of the field of vision is also found in primary microteleopsia. The fact, however, that in both patients the unilateral microteleopsia was combined with a homolateral microstereognosia indicates the activity of some more basic mechanism. The observation that the recorded disturbed handwriting also appeared after elimination of visual control, when both eyes were closed, supports this assumption.

SUMMARY

In two patients with the sensorimotor induction syndrome in left-sided disequilibrium an ipsilateral microteleopsia was

found. This disturbance was also reflected in the crowded handwriting of the first patient, and in the reduction in size of the drawings of the second patient. The microteleopic phenomena were systematically influenced by colors, in that blue caused their amelioration, while red aggravated them. The microteleopsia found in these patients, and which is systematically influenced by colors, is considered to be a secondary induced phenomenon in contrast to the primary microteleopsia encountered in anatomical lesions of the visual pathways.

REFERENCES

1. Bender, M. B. and Savitsky, N. Micropsia and teleopsia limited to the temporal fields of vision. Arch. Ophth., **29:** 904–908, 1943.
2. Goldstein, K. and Jablonski, W. Ueber den Einfluss des Tonus auf Refraktion und Sehleistungen. Arch. f. Ophth., **130:** 395–410, 1933.
3. Goldstein, K. and Rosenthal, O. Zum Problem der Wirkung der Farben auf den Organismus. Schweiz. Arch. f. Neurol. u. Psychiat., **26:** 3–26, 1930.
4. Halpern, L. Additional contributions to the sensorimotor induction syndrome in unilateral disequilibrium with special reference to the effect of colors. J. Nerv. & Ment. Dis., **123:** 334–350, 1956.
5. Halpern, L. Spontaneous and induced convulsions in unilateral disequilibrium. Psychiat. et neurol., **133:** 29–39, 1957.
6. Halpern, L. and Feinmesser, M. The variability of the threshold of acoustic discomfort in the sensorimotor induction syndrome with special reference to the effect of colors. Confin. neurol., **16:** 309–320, 1956.
7. Halpern, L. and Kugelmass, S. The variability of reaction time in the sensorimotor induction syndrome with special reference to the effect of colors. J. Psychol., **41:** 255–269, 1956.
8. Halpern, L. and Kugelmass, S. The variability of tactile two point discrimination in the sensorimotor induction syndrome. Acta psychol., **13:** 162, 1957.
9. Halpern, L. and Kugelmass, S. The variability of vibratory perception in the sensorimotor induction syndrome. Acta psychiat. et neurol., **33:** 181–192, 1958.
10. Halpern, L. and Landau, J. The visual field in the sensorimotor induction syndrome and its changes under the influence of colors. J. Nerv. & Ment. Dis., **124:** 487–491, 1956.
11. Halpern, L., Braun, K. and Eliakim, M. Induced respiratory and circulatory changes in unilateral disequilibrium. Am. J. Cardiol., **2:** 334–341, 1958.
12. van Bogaert, L. Attaques de microtéleopsie, attaques uncinées avec hemianopsie quadrantale homonyme par gliome de la région temporale, sans stase papillaire. J. de neurol. et de psychiat., **28:** 1928.

FUNCTIONAL ORGANIZATION OF THE BRAIN, PAST AND PRESENT

HAROLD E. HIMWICH, M.D.[1]

The problem of behavior has occupied a position of central importance for many years and despite many significant advances, still continues to baffle us. A great step forward was achieved by Hughlings Jackson (18) when he proposed that a lesion of the brain makes itself manifest symptomatologically by two categories of behavioral alterations; the first being the expression of the loss of the activities of the injured areas, and the second representing the result of the release of functions of other parts of the brain. With the phyletic development of the brain, as it spread in a cephalad direction, broader and less specific functions had superimposed upon them more specific sensory discrimination and a finer execution of motion. Thus, cephalad dominance is characterized by elements of inhibition as well as by selective facilitation. We now have much evidence for the conception that various cerebral structures and their connecting pathways represent facilitatory, positive feed-backs and inhibitory, negative circuits. Though cerebral mechanisms are more complicated than previously surmised, Jackson's original concept of cerebral functions still holds. Thus the loss of a single brain area interferes with the functions of one or more feed-backs in the competition of various circuits for the control of movement. Yet the subsequent behavioral changes occur in characteristic patterns as muscular activities become less discriminative and lower thresholds develop for coarser stimuli. More recently the researches of Moruzzi and Magoun (26), as well as Jasper (19) and Bremer (3), initiated another viewpoint of the functional organization of the brain. If the conception of Hughlings Jackson may be considered that of a horizontal organization, the newer one might be characterized as vertical (Figure 1). As emphasized by Livingston, Haugen and Brookhart (25), the central nervous system may be regarded as divided into three vertical columns extending throughout the entire length of the central nervous system: the first includes ascending spinal pathways carrying sensory impulses that are relayed by the thalamus to specific sensory areas of the cortex. The second column consists of the descending motor pathways of the corticospinal tracts. Between these two is a third composed of indirect connections: association areas of the cerebral cortex, the reticular formation of the brainstem and the extrapyramidal motor tracts descending to the anterior horn cells of the spinal cord. The third column also possesses ascending functions in the two parts of the activities of the reticular formation (30, 31) which are continued by the diffusely projecting thalamocortical unspecific projections. A third viewpoint is that of the Vogts' (38), whose studies revealed that injurious substances may affect the various cerebral areas in such selective manner as to indicate that some are especially susceptible to a given toxic substance. They suggested a physiochemical basis to explain the greater sensitivity exhibited by some brain structures in comparison with others. More recently the histochemical researches of Cammermeyer and Swank (4, 35) revealed additional evidence for the third type of stratification of cerebral functions, for example, anesthesia with barbiturates and convulsions due to pictroxin produce selective injuries in the cerebral neurons of dogs.

It is the chief purpose of this communica-

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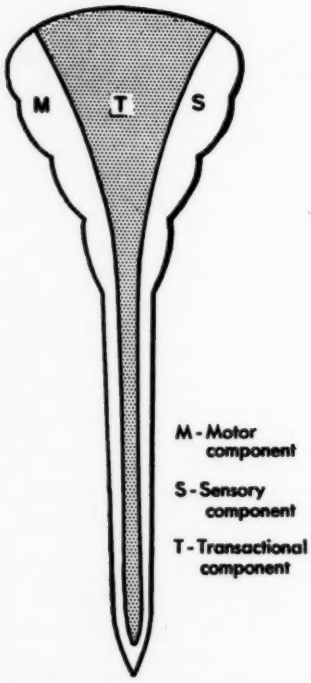


FIG. 1. The activities of the structures forming the transactional component (T) of the central nervous system find their expression via final common projections in the caudal reticular formation. Such activities may be initiated by the sensory input (S) and attain motor expression (M) but have an identity of their own which is greater than the sum of the two component parts (25).

tion to determine the relationships between these three viewpoints and to ascertain to what extent they may be either complementary or contradictory to each other. For this analysis two different kinds of observations will be used. The first will include the effects of acute deprivation of energy from the brain whether by hypoglycemia or anoxia. For the second, the actions of tranquilizing drugs and especially reserpine and chlorpromazine will be studied. In both instances behavioral as well as biochemical alterations will be used as indicators to assay the effects of these procedures and drugs upon the brain.

The behavioral changes occurring in Sakel's insulin hypoglycemia treatment for schizophrenics (33) can be explained in part by the application of Jackson's horizontal arrangement of brain functions. The hypoglycemia symptoms which occur in the sequence of five groups or phyletic phases (Figure 2) have been fully described elsewhere (11) and only those pertinent to our present analysis will be mentioned. In the first phase of insulin hypoglycemia, perception and thinking, as indicated by the vague and incoherent responses to simple questions, become increasingly impaired. The clouding of consciousness gradually deepens until environmental contact is lost with the suppression of the cortical components of various functions. The second stage of insulin hypoglycemia is characterized by release of subcorticodiencephalic structures with the appearance of primitive movements—involuntary grasping and sucking, protrusion of the tongue, hissing, snarling and grimacing. Myoclonic twitching and clonic spasms are also observed. At the end of the second phase characteristic hypoglycemic convulsions are observed in almost half of the hypoglycemic patients. More fre-

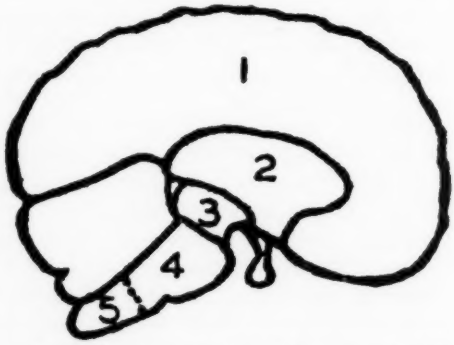


FIG. 2. Transverse section of brain revealing the five layers to which the symptoms of hypoglycemia have been allocated. 1) cerebral cortex, the depression of which brings on the cortical phase in hypoglycemia; 2) the subcortico-diencephalon, responsible for the symptoms of release in the second phase; 3) the mesencephalon involving the symptoms of the third phase; 4) the pons and the rostral portion of the medulla (upper) and 5) the caudad portion of the medulla (lower), releasing the premyencephalic and myencephalic symptoms respectively (11).

quently, the patient passes on directly to the release of the tonic and torsion spasms of the third, mesencephalic phase and then to the extensor spasms of the fourth, premyencephalic phase. Finally, all motor activity ceases as the patient sinks in the fifth or myelencephalic phase of insulin hypoglycemia. Though this symptomatology is in conformity with a phyletic regression which proceeds in accordance with the horizontal functional organization of the brain, we also recognize in the behavioral manifestations the activities of a vertical cerebral stratification. In the first phase of hypoglycemia, pyramidal and extrapyramidal cortical functions are first depressed and then eliminated. Thus, all the ensuing motor phenomena are of subcortical origin and gain expression in the reticulo-spinal, the vestibulo-spinal and other extrapyramidal pathways. The hypoglycemia convulsions appear at the time of the release of the mesencephalic reticular formation. In the fourth phase the suppression of the midbrain reticular formation removes constraints usually exerted upon bulbar areas both facilitatory and suppressor. The effects of the latter, however, are masked by those of the former and we witness the posture of decerebration in the human hypoglycemic subjects.

In general the motor manifestations of hypoglycemia and acute anoxia (1) follow the same pattern of phyletic regression. When a patient inhales nitrogen gas he rapidly passes through the first phase and loses contact with the environment. During the second phase there are myoclonic twitchings and a brief period of contractions of all four extremities. In the third stage, tonic and torsion spasms are seen and in the fourth either opisthotonos or emprosthotonos are observed, signs of decerebrate rigidity. In Figure 3, taken from a paper of Gastaut and Fischer-Williams (8), electrical events are illustrated in accordance with both horizontal and perpendicular schemes. Though they portray the changes of acute anoxia, they also apply to hypoglycemia. When extensor spasms are about to take place, the electrical activity has disappeared from the cortex as well as from the thalamocortical level. There are, however, slight residual activities in the hypothalamus and mesencephalon where electrical rhythms remain because oxidative metabolism may not fully be suppressed. The motor phenomena represented by the arrows, depend upon the operation of the caudal reticular formation when it is no longer subject to the control of higher nervous centers.

We will now turn to an examination of laboratory data obtained both on animals and man, not only to cast additional light on the phenomena of hypoglycemia and anoxia but to afford a deeper analysis of their mechanisms. These studies reveal that underlying the symptomatology of hypoglycemia and acute anoxia are the interactions of a metabolic gradient with deficiencies either of oxygen or blood sugar. This gradi-

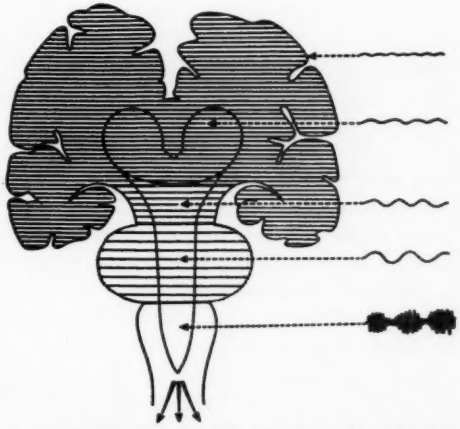


FIG. 3. Schematic presentation of the mechanism of anoxic convulsions. The density of the horizontal lines is proportioned to the intensity of the hypoxia, most marked in the cerebral hemispheres and least in the caudal reticular formation. The functional expression of this depression is revealed in the characteristics of the brain waves, the alpha-type rhythm has disappeared completely in the cerebral hemispheres while the caudal reticular formation reveals normal electrical activity (8).

ent, which is a result of diminishing intensity of metabolism spreading from the cerebral cortex toward the medulla oblongata, accounts in part for the observed behavioral changes. It is obvious that oxygen lack depresses brain metabolism with that of the rest of the body. The high rate of cerebral metabolism and its close minute-to-minute dependence on oxygen account for the brief period in which the series of anoxic symptoms are initiated and come to a culmination.

The symptoms of hypoglycemia also reveal the metabolic gradient in the brain in the production of behavior changes. In contrast to anoxia, however, a paucity in blood sugar seems to exert a selective action on the brain rather than upon the body as a whole. The explanation of this selectivity is supplied by observations revealing that the respiratory quotient of the brain is close to unity (15, 23). Such a value might indicate the exclusive oxidation of carbohydrate by the brain but subsequent work has revealed amino acids, nucleic acids and phospholipids can be metabolized in that organ (9). But their rates of utilization are not adequate to support brain metabolism which therefore falls during hypoglycemia (13, 21). Moreover, noncarbohydrates burned by the brain can be resynthesized only at the expense of the oxidation of carbohydrates (9). Thus, in the continued absence of glucose noncarbohydrates decrease as they cannot be reconstructed in the brain.

Observations supporting the conception of a metabolic gradient in the brain are many and only a few examples will be mentioned. Evidence obtained in the oxygen consumption of the various parts of the brain in the Warburg apparatus yielded additional support for the conclusion of differential metabolic rates with lesser demands for oxygen in each succeeding caudad region. For example, in the adult dog the telencephalic areas (Figure 4), the caudate nuclear and the cerebral gray matter enjoy the highest rate of oxygen consumption, the mesencephalic thalamus comes next, while the myelencephalic structure, the medulla, exhibits the lowest utilization of oxygen (14). The same order, in general, applies to the anarobic elaboration of energy with the formation of lactic acid. Both in adult cats and dogs the cortex comes somewhat below the caudate nucleus, which exhibits the most rapid rate. Then in descending order are the thalamus, the corpora quadrigemina, the cerebellum, the medulla and the cord (5). The effects of hypoglycemia upon such a metabolic hierarchy are observed by the pattern in which glycogen is depleted in the brain of dogs. The higher parts with their greater demands are associated with a loss of glycogen which, in general, proceeds from the newer to the older cerebral areas (6) (Figure 5). Additional evidence that the cerebral cortex works at a higher rate of activity and, therefore, has greater emergetic demands was disclosed with the aid of the electroencephalogram. The spontaneous electrical activity of the anterior and posterior hypothalamic leads continued after that of the cortex had disappeared in hypoglycemic dogs (16) (Figure 6). It is significant that hypoglycemic convulsions can take place in the decerebrate animal sectioned through the mesencephalon. To quote Olmsted and Logan (27), "Typical insulin convulsions can be induced in decerebrate cats . . .". We may therefore conclude that hypoglycemic convulsions are the functional expression of structures in the caudal brainstem.

The use of anoxia has also provided data of caudal reticular release due to functional cessation of suprabulbar areas. Ward and Wheatley (40) injected sodium cyanide into cats and monkeys (Figure 7), and reported that the electrogram of the cerebral cortex was the first to disappear. The elimination of the spontaneous potentials was observed next in diencephalic structures and shortly thereafter in the midbrain. In contrast, the bulbar reticular formation continued to function during the ensuing decerebrate

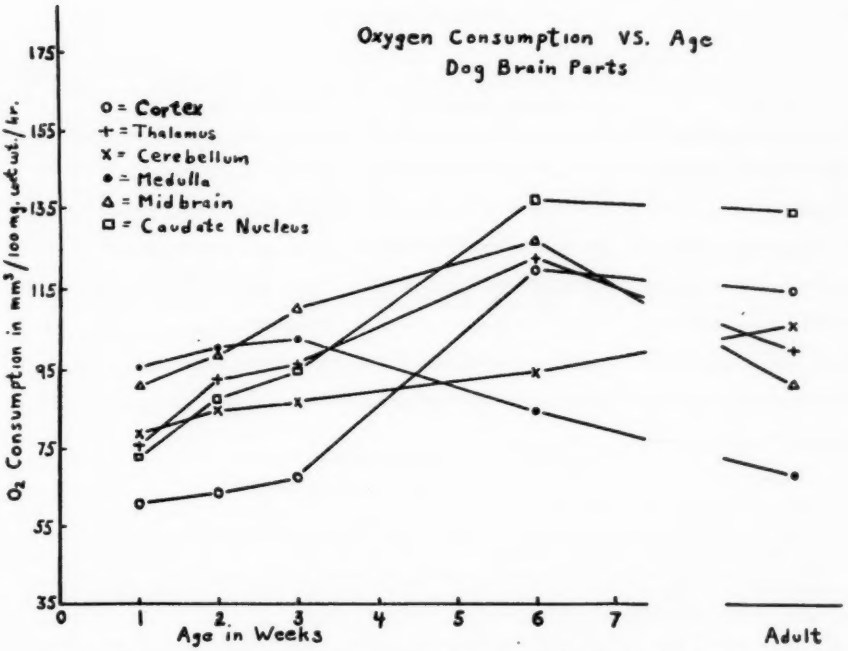


FIG. 4. The oxygen consumption of the various parts of the dog brain at 1, 2, 3, and 6 weeks and adulthood. In the adult animal the order in the intensity of oxygen consumption decreases as follows: caudate nucleus, cerebral cortex, cerebellum, thalamus, midbrain, medulla oblongata (14).

TABLE 1

Glycogen content (mg. %) of parts of the central nervous system of hypoglycemic dogs.*

No. of Exper.	Caudate	Corpora quadri-gemmina	Cerebral grey	Thalamus	Cere-bellum	Medulla	Cord
			Hypoglycemia				
1.	8	26	56	45	40	35	46
2.	12	28	35	40	32	26	14
3.	8	32	21	27	33	24	14
4.	1	8	16	8	30	49	122
5.	20	0	11	18	18	36	45
6.	12	13	19	20	8	19	16
7.	6	15	10	8	1	31	43
8.	0	0	2	0	1	31	32
9.	0	2	6	0	6	13	26
			Normal				
Aver.	58	50	73	62	35	37	29
Range	44-71	37-60	45-108	41-68	23-46	21-47	15-31

* Taken from Chesler and Himwich.[11] The observations of nine experiments are presented in the table. A heavy line has been drawn to separate the glycogen contents of the animals into two divisions. The values to the left of the heavy line are significantly lower than the lowest values for the normal range for that same part, while those to the right are not significantly lower than the normal. In general the upper parts of the brain lose their glycogen deposits before the lower areas are depleted.

FIG. 5. The observations of nine experiments on the effect of insulin hypoglycemia upon brain glycogen are presented. A heavy line has been drawn to separate the glycogen contents of the animals into two divisions. The values to the left of the heavy line are significantly lower than the lowest value for the normal range for that same part, while those to the right are not significantly lower than the normal. In general, the upper parts of the brain lose their glycogen deposits before the lower areas are depleted (6).

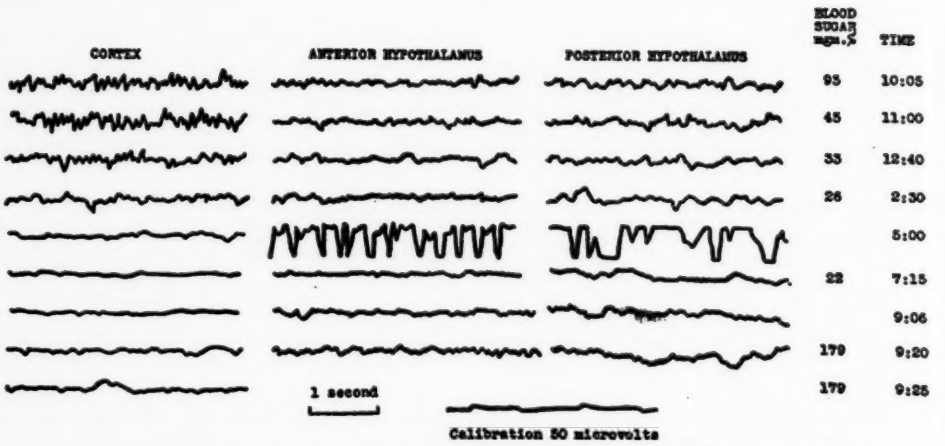
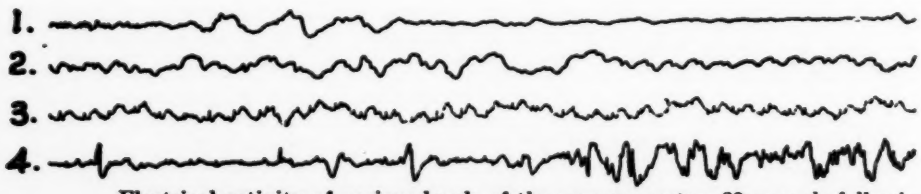


FIG. 6. Records from cortex, anterior hypothalamus and posterior hypothalamus during insulin hypoglycemia and recovery. Note decrease of rapid cortical waves which is marked at 2:30 and virtually complete at 5:00. The violent responses of the hypothalamus at that time produce amplifier block. These hypothalamic surges in turn give way to the hypoglycemic process. Sugar was given from 9:04 to 9:16 and recovery of hypothalamic leads is noted at 9:20 with beginning improvement in cortical leads as well (16).



Electrical activity of various levels of the nervous system 30 seconds following intravenous injection of 0.8 mg./kg. of NaCN. 1) Bifrontal cortex. 2) Hypothalamus. 3) Medial vestibular nucleus. 4) Ventral horn of lumbar cord.

FIG. 7. Electrical activity of various levels of the nervous system 30 seconds following intravenous injection of 0.8 mg./kg. of NaCN. 1) Bifrontal cortex, 2) Hypothalamus, 3) Medial vestibular nucleus, 4) Ventral horn of lumbar cord. Electrical activity fails in the cortex about 30 seconds after injection with sodium cyanide. The hypothalamus and medial vestibular nucleus maintain their electrical potentials while those in the ventral horn of the lumbar cord are increased in frequency and exaggerated in amplitude (40).

rigidity, while that of the gray matter of the cervical and lumbar cords showed a tremendous increase in both frequency and amplitude. Ward (39) was also able to show that the decerebrate state produced by sodium cyanide could be prevented by lesions which selectively destroyed the facilitatory region in the pontile tegmentum. All these observations taken together indicate the part played by the reticular formation in producing the motor phenomena of hypoglycemia and acute anoxia.

Important for our understanding of the reticular reactions is a measure of its metabolic rate, but such determinations are not available. We, however, possess indirect evidence obtained by examination of electrical activity in the reticular formation which indicates relative rates in comparison with those of other brain structures. Thus,

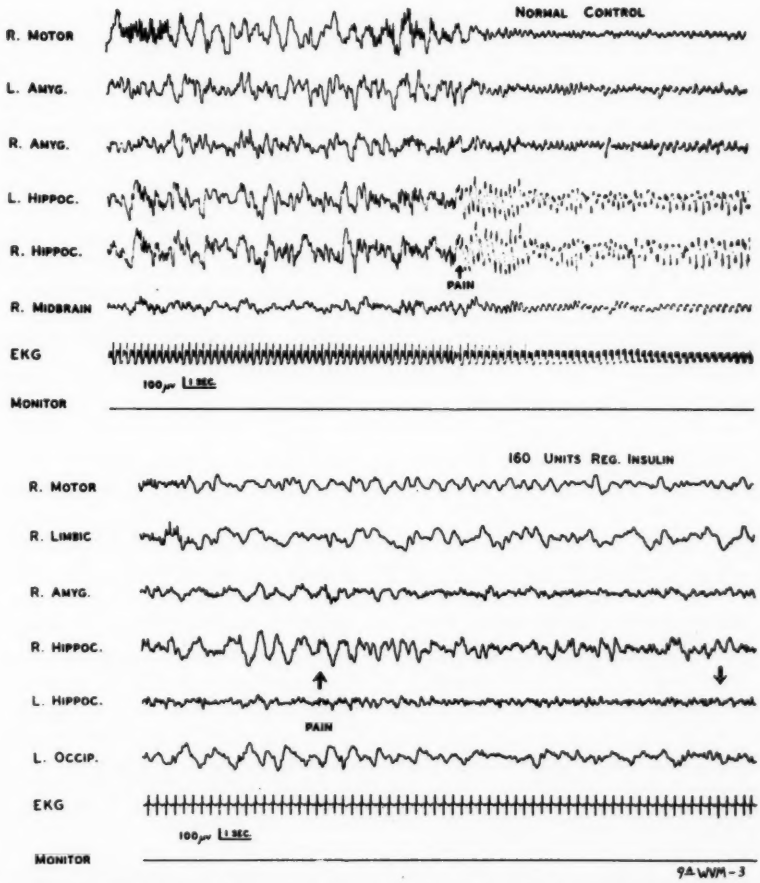


FIG. 8. Failure of arousal response after painful stimulation (lower group of tracings) as compared with normal response (upper group of tracings). Note that the normal response to pain disappears while cortical electrical activity continues during hypoglycemia. Abbreviations employed in this and in subsequent figures are as follows: R. or L. Motor, right or left motor cortex; R. or L. Limbic, right or left limbic cortex; R. or L. Occip., right or left occipital cortex; R. or L. Amygd., right or left amygdala; R. or L. Hippoc., right or left hippocampus; R. or L. Midbrain, right or left midbrain area; EKG, electrocardiogram; Monitor, monitor deflection indicating photic "flash" stimulation (37).

we have observed that the EEG activation resulting from painful stimuli fails before the spontaneous EEG of the hypoglycemic rabbit (Figure 8). Further analysis reveals that the extinction of EEG alerting is a complex phenomenon (37). In the intact animal the metabolic support of EEG activation depends not only on the metabolic rate of the reticular formation but also on that of the various cortical and subcortical areas involved in the alerting reaction. Furthermore, the effects of the resting metabolism of this system are stepped up during the EEG arousal. That the reticular formation is not necessarily suppressed in the absence of EEG alerting (Figure 9) is made

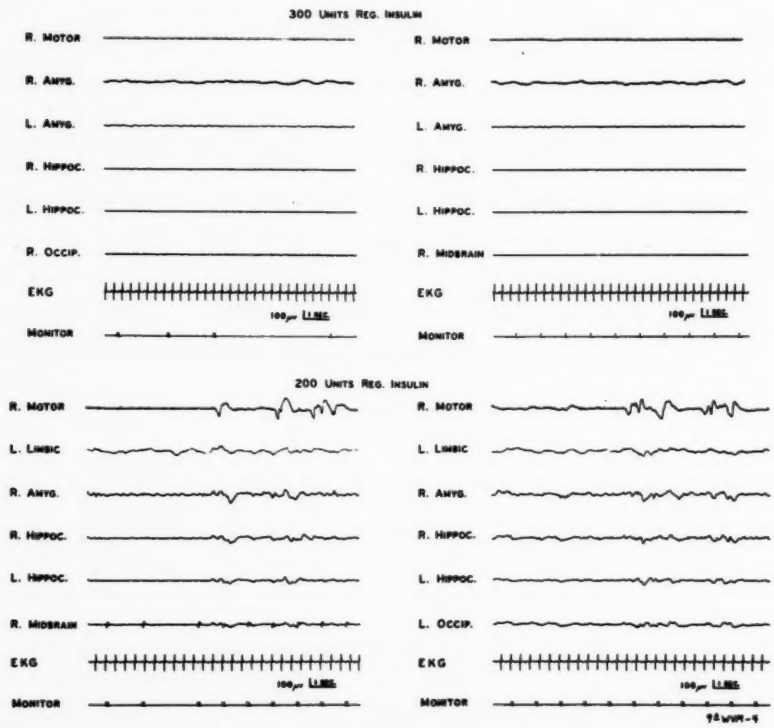


Fig. 9. Four groups of brain waves of rabbits in deep hypoglycemia. The upper two groups represent failure of response to photic stimulation. The lower group of tracings was obtained by repeatedly switching from midbrain to occipital cortex leads. The lower left group shows response to visual stimulation in midbrain, whereas occipital cortex (lower right) fails to react (37).

evident by the retention of the ability to respond to visual stimulation both in the occipital cortex and in the midbrain. A subcortical pathway which mediates such responses has been identified with the activity of the unspecific reticulothalamic pathway for the visual modality (17). These visual responses finally also give way as hypoglycemia deepens and disappear first in the cortex and then in the midbrain.

Data derived from the reticular formation have been offered by Ward and Wheatley (40) when they inserted electrodes into the different cerebral areas and were thus able to follow their spontaneous activities when acute anoxia was evoked by poisoning with cyanide. They noted that the electrical potentials of the midbrain reticular formation disappeared simultaneously with those of other midbrain structures. They also found that the bulbar reticular formation continued its activities after those of the midbrain had been suppressed, a phenomenon in agreement with observations on the simultaneous release of all bulbar functions. Thus, this indirect evidence indicates that the metabolism of a given area of the reticular formation closely approaches that of the horizontal layer through which it traverses. Such a suggestion is implicit in the conception that both horizontal and vertical organizations operate simultaneously. In fact, the horizontal stratification of the brain can function only

because of the vertical arrangement necessary to integrate that organ into a harmoniously acting unit. In a sense they are complementary to each other as each viewpoint contributes in part to the explanation of the motor manifestations of hypoglycemia and acute anoxia. It is obvious that the thalamocortical projections and the reticular formation, parts of the perpendicular scheme, must necessarily also occupy positions in the horizontal organization of the brain.

We shall now return to the suggestion of the Vogts' (38), namely that of the pathoclisis or specific susceptibilities to chemical agents. The specific susceptibility exhibited during hypoglycemia and acute anoxia is different, for example, from that observed with the lenticular destruction in carbon monoxide poisoning. The mechanism of the latter is unknown, but both in sugar and oxygen lack, the alterations are results of energy deprivation in structures with graded energy demands. The observation that cephalad areas are more susceptible to energy lack than are the caudal regions is one form of pathoclisis. In those two instances phyletic regression and specificity operate simultaneously. In fact, neither the horizontal nor the vertical organization could be disclosed were it not for this metabolic form of pathoclisis. We thus have evidence for three different explanations for the changes in brain function during hypoglycemia and anoxia.

The actions of the psychopharmacologic agents with their selectivities reveal repeated examples of pathoclisis. Under the influence of reserpine first the amygdala and then other rhinencephalic structures are stimulated, disclosing spikes which culminate in seizure patterns (22) (Figure 10). Chlorpromazine, another tranquilizer, facilitates a similar development of rhinencephalic spikes and seizure patterns (29) (Figure 11). Imipramine hydrochloride, and antidepressant drug, which also occasionally acts as a tranquilizer, provides still another example of drug pathoclisis. Spiking first induced in the hippocampus may spread in a manner similar to that of the other two drugs and culminate in convulsant patterns (Figure 12) (36). It is of more than passing interest that insulin hypoglycemia, which also produces beneficial effects in schizophrenia, shares the characteristics of the tranquilizers to provoke rhinencephalic seizures (Figures 13, 14) (37). It is not improbable that seizures deprive the brain part they occupy of its normal functions. The loss of the contributions of the amygdala or hippocampus would thus interfere with a circuit proposed by Papez (28) to serve as a portion of the anatomical substrate for emotion. Impulses from the entorhinal cortex and hippocampus proceed successively through the fornix to the mammillary bodies, the anterior thalamic nuclei, the cingulate gyrus and return via the cingulum to the hippocampus (Figure 15) (28).

In the function of this circuit the neocor-

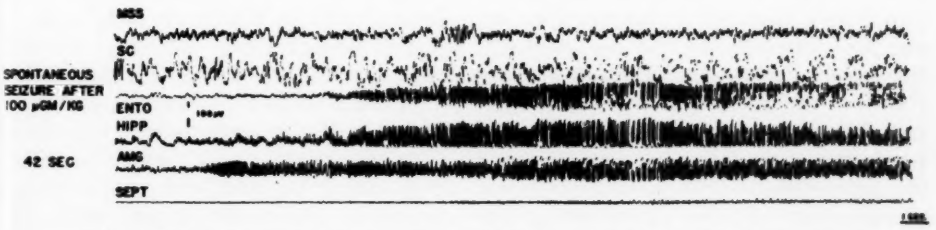


FIG. 10. Effect of reserpine (0.1 mg./kg.) on brain waves of cat; records of spontaneous rhinencephalic seizures initiated in the amygdala (AMG). Note extension of convulsive patterns to other limbic structures: hippocampus (HIPP), entorhinal gyrus (ENTO), and septum (SEPT). However, the neocortex (MMS and SC) remains free of such abnormalities (22).

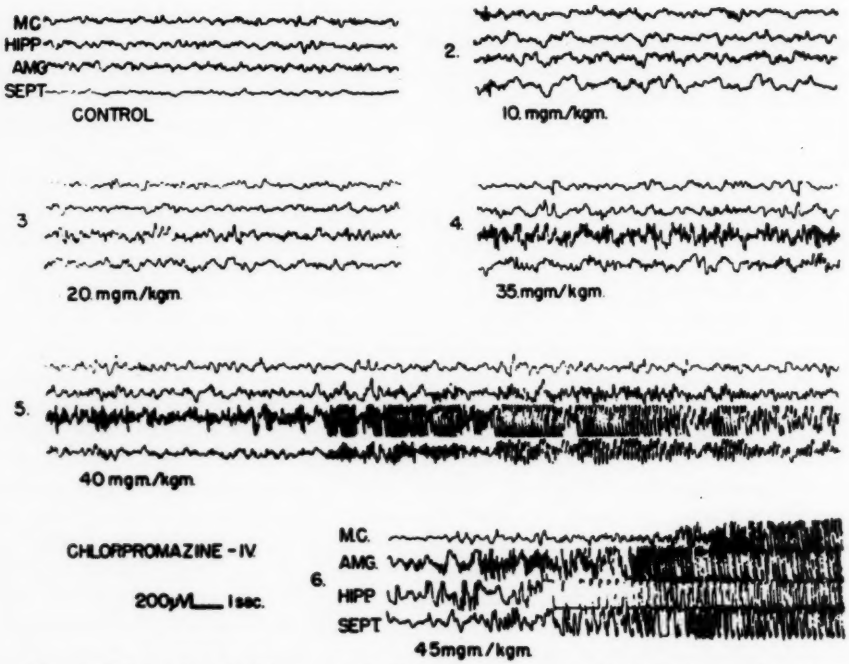


FIG. 11. Effects of gradual increases of chlorpromazine upon cat brain. Seizure spiking is initiated in amygdala (AMG) (part 4 of Figure) at time when motor cortex (MC) is not affected. With gradually increasing doses of chlorpromazine seizure activity spreads throughout rhinencephalic structures, hippocampus (HIPP), and septum (SEPT) before finally involving the motor cortex (MC) (29).

tex, by way of the cingulate gyrus, adds discriminative aspects of consciousness to the crude awareness afforded by the older rhinencephalic structures more closely associated with emotion including, with the hippocampus, the septal area and the amygdaloid nuclei. Seizures which provoke a functional ablation of the hippocampus and amygdala can interfere with the activity of this circuit. Rothfield and Harman (32) report that the decrease of the threshold to rage following decortication depends upon transection of the fornix in accordance with the conception of Papez. The emotional changes observed after extirpation of the septal region and the amygdala, hippocampus and fornix with the release of the hypothalamic functions may also be adduced as tentative evidence in favor of this feedback. Perhaps the hallucinatory and delusional experiences with their emotionally tinged ideation suffered by schizophrenic patients are relieved by the interruptions of this circuit (12). In that case the rhinencephalic seizures may be a cause of the antipsychotic effects of the tranquilizing drugs as well as those of hypoglycemia.

Mechanical, chemical and electrical stimulation (2, 24, 10), drug action (22, 29, 36) and hypoglycemia (37) all evoke selectively hippocampal or amygdaloid convulsive electrical patterns. Such convulsions, however, cannot be attributed exclusively to stimulation. In insulin hypoglycemia, for example, a seizure taking place in the paleocortex may rather be regarded as a release from the neocortical restraints (Figures 13, 14) (37). These hypoglycemic seizures are

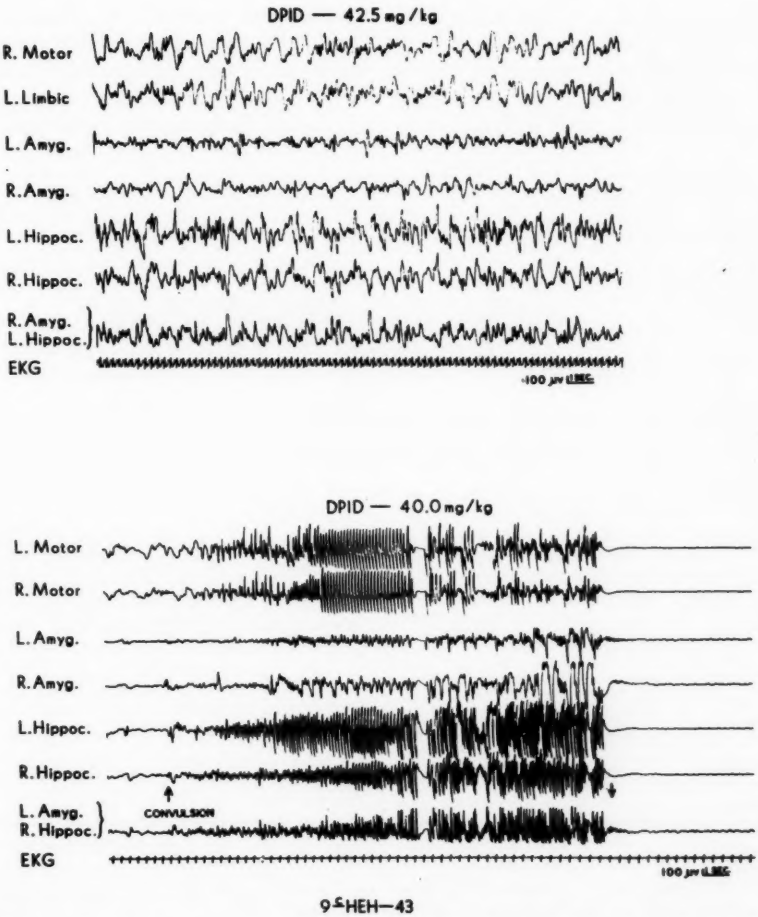


FIG. 12. Preconvulsant doses of imipramine (DPID) in a rabbit evoke spike-like brain waves predominant in the hippocampus (upper group of tracings). Spiking is followed by convulsant brain patterns spreading to all leads (lower group of tracings) (36).

observed after the spontaneous EEG has disappeared and therefore, adhere to Hughlings Jackson's horizontal scheme. But rhinencephalic convulsive patterns also take their part in the concept of perpendicular organization as the reticular formation is connected with rhinencephalic structures. For example, the olfactory tubercle receives impulses from the midbrain reticular formation. The rhinencephalon is also connected to the reticular formation. Thus the function of the Papez circuit is closely associated with that of the reticular formation (Figure 15).

When we considered hypoglycemia and acute anoxia, we saw the same bits of behavior viewed from three different aspects, each one describing the same phenomena in terms, however, of different coordinates, each one adding information and clarification in regard to underlying mechanisms. We have also found that the phenomenon

of rhinencephalic susceptibility to drug-induced seizures may be analyzed from each of these three viewpoints with equal validity and advantage. Together, the three viewpoints add up to a better understanding of observed behavior. It therefore seems that each viewpoint presents a different facet of the same phenomenon, a situation which leads to inquiry as to the nature of this central core, and in each instance it is

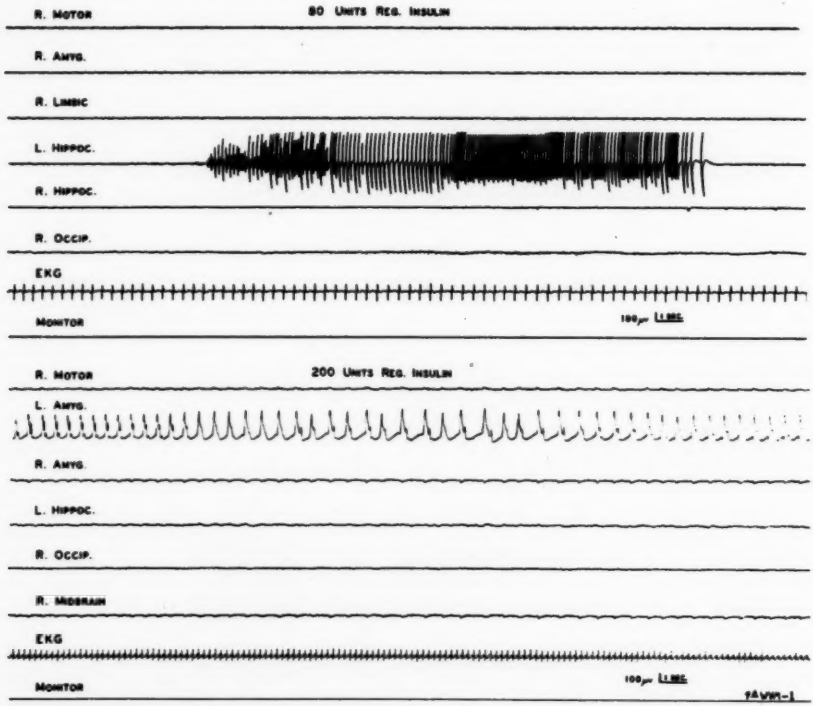


FIG. 13. Hypoglycemic convulsant discharges are confined to the left hippocampus (upper group of tracings) and left amygdala (lower tracings) (37).

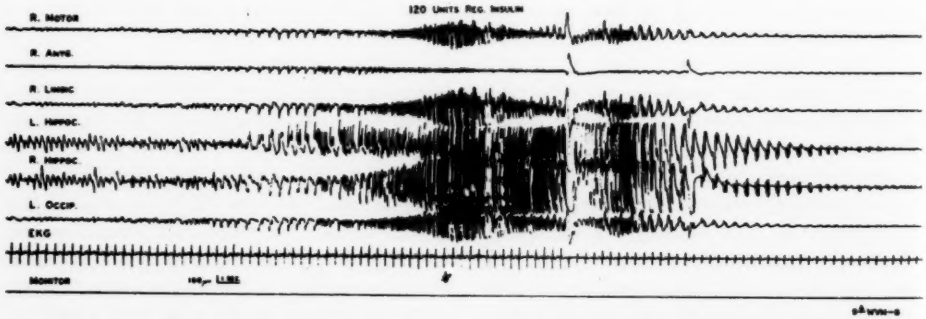


FIG. 14. Progressive hypoglycemic seizure pattern. Note the onset in the hippocampal tracings and extension to other rhinencephalic and cortical leads. Finally, the seizure pattern regresses (37).

referable to a break in cerebral feed-back mechanisms. In hypoglycemia and acute anoxia such breaks occur from above downward. In the case of the psychopharmacological drugs, the rhinencephalon is a site of the failure in function. In such a highly integrated organ as the brain, composed of so many interdependent structures, it would be strange indeed if the loss of any area would not interfere with cerebral feed-back mechanisms. It is this interference which is responsible for what Hughlings Jackson (18) has termed release phenomenon, and which now is more generally referred to as a failure in cerebral feed-back mechanisms. As an example of the reverberating circuits is a suggestion of Jung and Hassler (20) that the pyramidal tract may function as one of the efferent pathways of the extrapyramidal system. Impulses pass from the cerebellum via the brachium conjunctivum to the thalamus and area 4 gamma where cortico-spinal fibers originate. From area 4 gamma cortico-pontine tracts also carry impulses to the oral pontine ganglia and complete the circuit as they attain the anterior lobe of the cerebellum. The cerebellum which receives impulses from the spinal-cerebellar tracts contains the mechanisms coordinating not only with the cortical motor system but also the various extrapyramidal centers including the reticular formation of the pons and the vestibular nuclei. These suggestions portray a present viewpoint of the interdependence of the various brain areas.

This paper is dedicated with admiration and affection to Ernest Spiegel on his 65th birthday. His work and that of his associates have shown that the central mechanism of the emotions depends upon an interplay of not one, but congeries of circuits: "(a) the connections of the dorsomedial nuclei with the frontal association areas, (b) the connections of the dorsomedial nuclei with the cingulate gyrus, (c) connections of the hypothalamus with the frontal lobe, (d) intradiencephalic connections chiefly between the dorsomedial nuclei and the hypothalamus, perhaps also between the anterior nuclei and the mammillary bodies" (34). This paper was prepared chiefly to afford additional examples of his ideas.

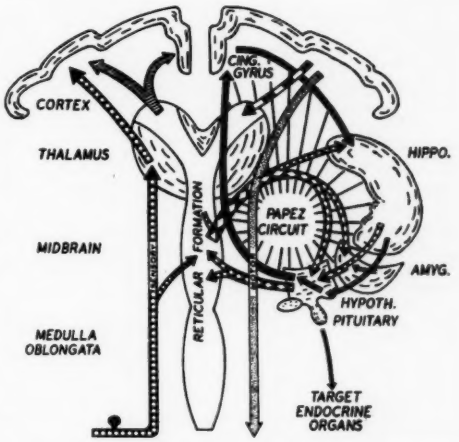


FIG. 15. The left half of this figure portrays specific sensory pathways to the thalamic sensory nuclei and the cortical sensory areas as well as a collateral (white dots on black arrows) to the reticular formation (white) which is continued to the diffuse thalamocortical projection (shaded). The reticular formation also possesses important descending motor activities. On the right side of the figure is indicated diagramatically (in black arrows) the Papez circuit connecting the hippocampus, fornix, hypothalamus (mammillary body) thalamus (anterior nucleus), cingulate gyrus and cingulum returning to the hippocampus. The connections of the Papez circuit with the amygdala and reticular formation are suggested by arrows containing white diamond shapes. Fibers originating in the nuclei of Gudden and Bechterev pass directly to the hypothalamus and to the septal area, not indicated, and thence to the hippocampus. The feed-back from the cortex to the reticular formation (white and black arrow) as well as the motor pathway from the cortex to the spinal column (stipled arrow) are also included in the right half of the diagram. This figure is adapted from Galambos (7).

REFERENCES

1. ALEXANDER, F. A. D. AND HIMWICH, H. E. Nitrogen inhalation therapy for schizophrenia. Am. J. Psychiat., **96**: 643–655, 1939.
2. ANDY, O. J. AND AKERT, K. Seizure patterns induced by electrical stimulation of hippocampal formation in the cat. J. Neuropath. & Exper. Neurol., **14**: 198–213, 1955.

3. Bremer, F. The neurophysiological problem of sleep. In *Brain Mechanisms and Consciousness*, Delafresnaye, J. F., ed. Thomas, Springfield, Ill., 1954.
4. Cammermeyer, J. and Swank, R. L. The effect of anaesthetics and picrotoxin on the tissue phosphatases in the cerebellum and olivary nucleus of the dog. Acta pharmacol. et toxicol., **7**: 65–82, 1951.
5. Chesler, A. and Himwich, H. E. Comparative studies of the rates of oxidation and glycolysis in the cerebral cortex and brain stem of the rat. Am. J. Physiol., **141**: 513–517, 1944.
6. Chesler, A. and Himwich, H. E. Effect of insulin hypoglycemia on glycogen content of parts of the central nervous system of the dog. Arch. Neurol. & Psychiat., **52**: 114–116, 1944.
7. Galambos, R. In *The Central Nervous System and Behavior*, Brazier, M. A. B., ed., pp. 287–293. Madison Printing Co., Madison, Wis., 1959.
8. Gastaut, H. and Fischer-Williams, M. The physiology of epileptic seizures. In *Handbook of Physiology*, Vol. 1, pp. 329–363. Am. Physiol. Soc., Washington, 1959.
9. Geiger, A. Chemical changes accompanying activity in the brain. In *Metabolism of the Nervous System*, Richter, D., ed., pp. 245–256. Pergamon Press, New York, 1957.
10. Green, J. D. and Shimamoto, T. Hippocampal seizures and their propagation. A. M. A. Arch. Neurol. & Psychiat., **70**: 687–702, 1953.
11. Himwich, H. E. *Brain Metabolism and Cerebral Disorders*. Waverly Press, Baltimore, 1951.
12. Himwich, H. E. Prospects in psychopharmacology. J. Nerv. & Ment. Dis., **122**: 413–423, 1955.
13. Himwich, H. E. and Fazekas, J. F. Comparative studies of the metabolism of the brain of infant and adult dogs. Am. J. Physiol., **132**: 454–459, 1941.
14. Himwich, H. E. and Nahum, L. H. The respiratory quotient of the brain. Am. J. Physiol., **90**: 389–390, 1929 & **101**: 446–453, 1932.
15. Himwich, H. E., Bowman, K. M., Daly, C., Fazekas, J. F., Wortis, J. and Goldfarb, W. Cerebral blood flow and brain metabolism during insulin hypoglycemia. Am. J. Physiol., **132**: 640–647, 1941.
16. Hoagland, H., Himwich, H. E., Cambell, E., Fazekas, J. F., and Hadidian, Z. Effects of hypoglycemia and pentobarbital sodium on electrical activity of cerebral cortex and hypothalamus (dogs). J. Neurophysiol., **2**: 276–288, 1939.
17. Hunter, J. and Ingvar, D. H. Pathways mediating metrazol induced irradiation of visual impulses. Electroencephalog. & Clin. Neurophysiol., **7**: 39–60, 1955.
18. Jackson, J. H. The Croonian lectures on evolution and dissolution of the nervous system. Brit. M. J., **1**: 591–593, 660–663, 703–707, 1884.
19. Jasper, H. Diffuse projection systems: The integrative action of the thalamic reticular system. Electroencephalog. & Clin. Neurophysiol., **1**: 405–419, 1949.
20. Jung, R. and Hassler, R. The extrapyramidal motor system. In *Handbook of Physiology*, Vol. 2, *Neurophysiology*, pp. 863–927. Am. Physiol. Soc., Baltimore, 1959.
21. Kety, S. S., Woodford, R. B., Harmel, M. H., Freyhan, F. A., Appel, K. E. and Schmidt, C. F. Cerebral blood flow metabolism in schizophrenia. The effects of barbiturate semi-narcosis, insulin coma and electroshock. Am. J. Psychiat., **104**: 765–770, 1948.
22. Killam, E. K. and Killam, K. F. The influence of drugs on central afferent pathways. In *Brain Mechanisms and Drug Action*, Fields, W. S., ed., pp. 71–98. Thomas, Springfield, Ill., 1957.
23. Lennox, W. G. The cerebral circulation. XIV. The respiratory quotient of the brain and of the extremities in man. Arch. Neurol. & Psychiat., **26**: 719–724, 1931.
24. Liberson, W. T. and Akert, K. Hippocampal seizure states in guinea pig. Electroencephalog. & Clin. Neurophysiol., **7**: 211–222, 1955.
25. Livingston, W. K., Haugen, F. P. and Brookhart, J. M. Functional organization of the central nervous system. Neurology, **4**: 458–496, 1954.
26. Moruzzi, G. and Magoun, H. W. Brain stem reticular formation. Electroencephalog. & Clin. Neurophysiol., **1**: 455–473, 1949.
27. Olmsted, J. M. D. and Logan, H. D. The effect of insulin on the central nervous system and its relation to the pituitary body. Am. J. Physiol., **66**: 437–444, 1923.
28. Papez, J. A. A proposed mechanism of emotion. Arch. Neurol. & Psychiat., **38**: 725–743, 1937.
29. Preston, J. B. Effects of chlorpromazine on the central nervous system of the cat: A possible neural basis for action. J. Pharmacol. & Exper. Therap., **118**: 100–115, 1956.
30. Rinaldi, F. and Himwich, H. E. Alerting responses and actions of atropine and cholinergic drugs. A. M. A. Arch. Neurol. & Psychiat., **73**: 387–395, 1955.
31. Rinaldi, F. and Himwich, H. E. Cholinergic mechanism involved in function of mesodiencephalic activating system. A. M. A. Arch. Neurol. & Psychiat., **73**: 396–402, 1955.
32. Rothfield, L. and Harman, P. J. On the relation of the hippocampal-fornix to the control of rage responses in cats. J. Comp. Neurol., **101**: 265–282, 1954.
33. Sakel, M. *Pharmacological Treatment of Schizophrenia*. Nervous & Mental Diseases, New York, 1938.
34. Spiegel, E. A., Wycis, H. T., Freed, H. and Orchinik, C. The central mechanism of the emotions (experiences with circumscribed

thalamic lesions). Am. J. Psychiat., **108:** 426–431, 1951.

35. Swank, R. L. and Cammermeyer, J. The selective effect of anesthetics and picrotoxin on the cerebral cortex of the dog: An electroencephalographic and histochemical study. J. Cell. & Comp. Physiol., **34:** 43–70, 1949.

36. Van Meter, W. G., Owens, H. F. and Himwich, H. E. Cortical and rhinencephalic electrical potentials during hypoglycemia. A. M. A. Arch. Neurol. & Psychiat., **80:** 314–320, 1958.

37. Van Meter, W. G., Owens, H. F., and Himwich, H. E. Effects of tofranil, an antidepressant drug, on electrical potentials of rabbit brain. Canad. Psychiat. A. J., **4:** S113–S119, 1959.

38. Vogt, O. Der Begriff der Pathoklise. J. Psychol. u. Neurol., **31:** 245–255, 1925.

39. Ward, A. A., Jr. Decerebrate rigidity. J. Neurophysiol., **10:** 89–103, 1947.

40. Ward, A. A., Jr. and Wheatley, M. D. Sodium cyanide: Sequence of changes of activity induced at various levels of the central nervous system. J. Neuropath. & Exper. Neurol., **6:** 292–294, 1947.

THE ACCURACY OF HUMAN STEREOENCEPHALOTOMY AS JUDGED BY HISTOLOGICAL CONFIRMATION OF ROENTGENOGRAPHIC LOCALIZATION

EDGAR M. HOUSEPIAN, M.D.[1] AND J. LAWRENCE POOL, M.D.

When Sir Victor Horsley (4) introduced a stereotaxic method for laboratory studies of the anatomy and physiology of the brain, he created a need and a challenge for the application of this technique to selective experimental and therapeutic stimulation or destruction of specific parts of the brain.

Dr. Spiegel, whose many contributions to the field of motor physiology are well known (10–12) is the pioneer who in 1947 introduced the use of stereotaxic principles to human neurosurgery. He demonstrated furthermore the practicality of utilizing internal cerebral landmarks visible on plain roentgenograms and pneumoencephalograms (15, 19). This obviated reliance on bony landmarks which are notoriously inconstant in the human species, and thus provided the necessary degree of theoretical and practical accuracy for the application of stereotaxic methods in man. Dr. Spiegel has thereby utilized this technique extensively for fundamental clinical contributions in the field of pathophysiology of the basal ganglia, thalamus and tegmentum (14, 16–18, 21–23).

The difficulties encountered in the stereotaxic method in the laboratory are well known, and despite assurance that there is little intraspecies variation in skull configuration and size, allowing the utilization of bony reference landmarks, the verification of stereotaxic placements in laboratory preparations shows a discomforting degree of inaccuracy (2). It is obvious that a variety of operational factors are responsible, as well as minor discrepancies in skull configuration from animal to animal.

Although it is acknowledged that the successful establishment of internal reference points has allowed progress in human stereotaxic surgery, the errors inherent in stereotaxic localization can still be discomforting, especially when there is distortion of cerebral landmarks by cerebral pathology (13).

Because autopsy confirmation of electrode placement and lesion localization is fortunately scarce, we have resorted to biopsy confirmation of our stereotaxic placements. The following report is an analysis of the accuracy of localization and placement of 34 lesions confirmed by histological study of tissue obtained by the use of a leukotome technique for the creation of lesions in the globus pallidus or thalamus.

MATERIALS AND METHODS

The present study constitutes an analysis of 34 tissue specimens obtained from 28 patients during the course of leukotome pallidectomy (pallido-ansectomy) or thalamectomy for Parkinsonism and a variety of dyskinesias. The landmarks used for localization as well as the principles utilized in controlling placement have been described in other publications (5, 7). The coordinates for the globus pallidus and thalamus are based on their relations to the anterior commissure, which is readily visualized by air encephalography, and are in agreement with those of other investigators (1, 9, 20). Instrument placement has been made under x-ray control which, in effect, rigidly enforces serial radiography. The instrument

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used for the creation of such surgical lesions and recovery of small amounts of tissue suitable for histological study is a specially constructed leukotome (Codman and Shurtleff, Boston, Mass.) having two flat blades which open into a sphere 1 centimeter in diameter. Additional features of this instrument are: 1) the leukotome blades can be replaced at operation by a plastic cannula which allows instillation of marking materials or drugs; 2) stimulating or recording electrodes can be interchanged by placement through the plastic cannula; and 3) electrolytic lesions can be made if desired. With this instrument approximately ½ gram specimens were obtained, formalin fixed, paraffin embedded and stained with H & E and Nissl.

RESULTS

Histological examination of these biopsy specimens showed 17 to be from the globus pallidus (Figure 1) and six from the thalamus (Figure 2). No pathological cellular changes were identified in these preparations. In six specimens nuclear elements suggesting globus pallidus as the site of origin were found but the quality of the fragments of tissue made positive identification questionable. There were five "negative" biopsies which showed only "cerebral white matter." These 23 biopsies of the globus pallidus and thalamus confirmed the clinical roentgenographic localization without, of course, indicating what portion of the respective structures were injured.

It is important to note that there was a profound degree of dilatation of the third ventricle in two of the cases with negative biopsies and that these lesions had been localized radiographically as being within the medial limits of the globus pallidus (Table 1). This supports pathological evidence indicating condensation and lateral displacement of the paraventricular structures when there is dilatation of the third ventricle.

Three other negative biopsies were related to errors of placement and localization in patients with roentgenographically normal brains. In two of these cases there was sudden hemiparesis which prompted immediate review of roentgenographic localization at the time of surgery. Errors were discovered and it was seen that the lesions were made in the region of the internal capsule. Resultant hemiparesis however gradually cleared, leaving only slight residual weakness. The final case, a youth with hemiparesis and abnormal involuntary movements since birth, also had a lesion clinically localized to the internal capsule. He showed a permanent abolition of his dyskinesia without increasing the hemiparesis and now is improved as to the use of his paretic and previously contorted extremity.

DISCUSSION

Of the 31 patients who showed evidence of objective improvement in tremor and/or rigidity, 23 had verified biopsy lesions of the globus pallidus or thalamus. Sixteen of the 31 showed *marked permanent* objective improvement despite the fact that positive biopsy confirmation was obtainable in only 14. Histological localization was questionable in two cases.

The group of four patients who showed marked initial but only transitory subsequent improvement following surgery are of interest. One had a Benedikt's syndrome and another a bizarre type of dystonia. Of the two remaining cases, both of whom had Parkinsonian tremors, a critical volume of destruction of the target structure may not have been achieved. Similar considerations may be responsible for explaining permanent but less dramatic results in ten other cases, five of whom had positive biopsy identification of the desired targets.

Analysis of these cases shows a high degree of correlation between permanent objective relief of tremor and rigidity and biopsy destruction of the medial portion of the globus pallidus (including the ventral

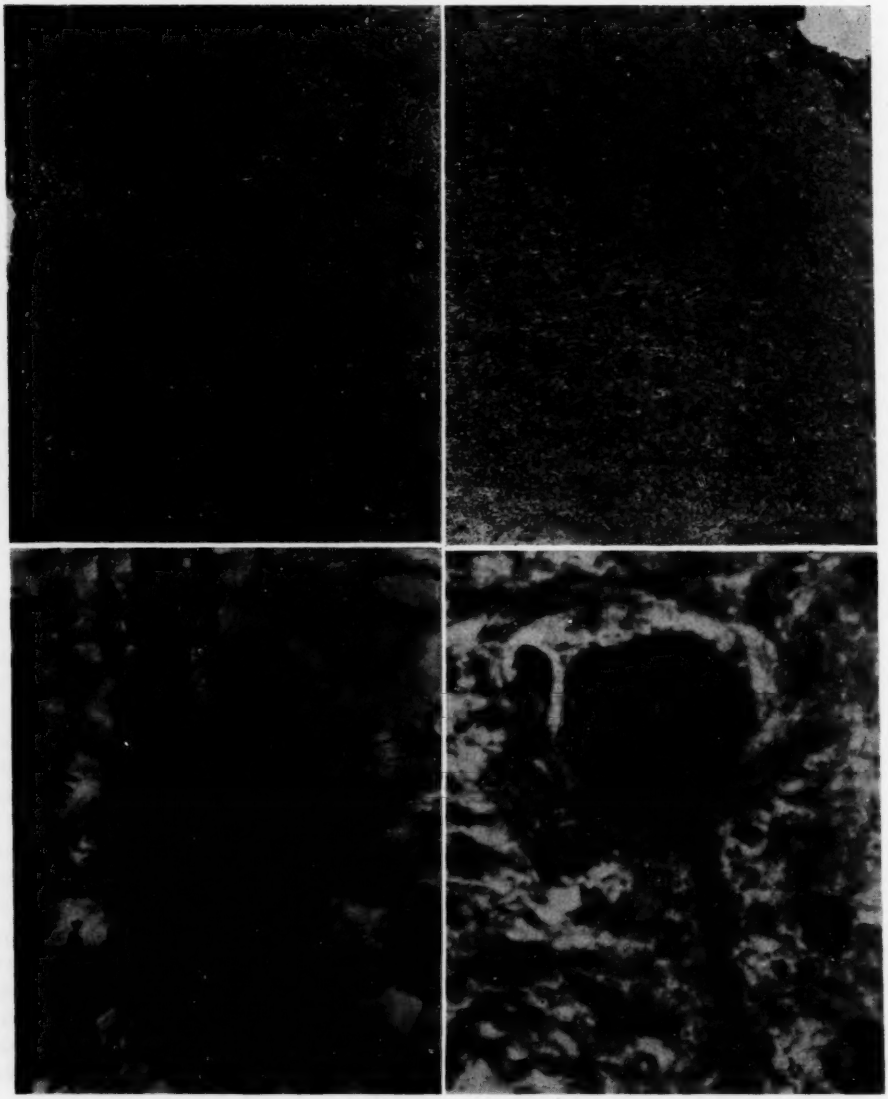

FIG. 1.(a) Biopsy specimens of globus pallidus; photomicrographs ×105. (H & E).
(b) Large neurons of globus pallidus; ×1750 (H & E).

division of the ansa lenticularis) or thalamus.

As we have repeatedly stressed (6, 8), however, objective postoperative improvement in tremor and rigidity unfortunately does not always imply a really beneficial postoperative result with respect to the clinical picture of Parkinsonism as a whole. This supports the contention that in some cases there are other disabling symptoms and signs characterized by faulty initiation and maintenance of willed activity (3).

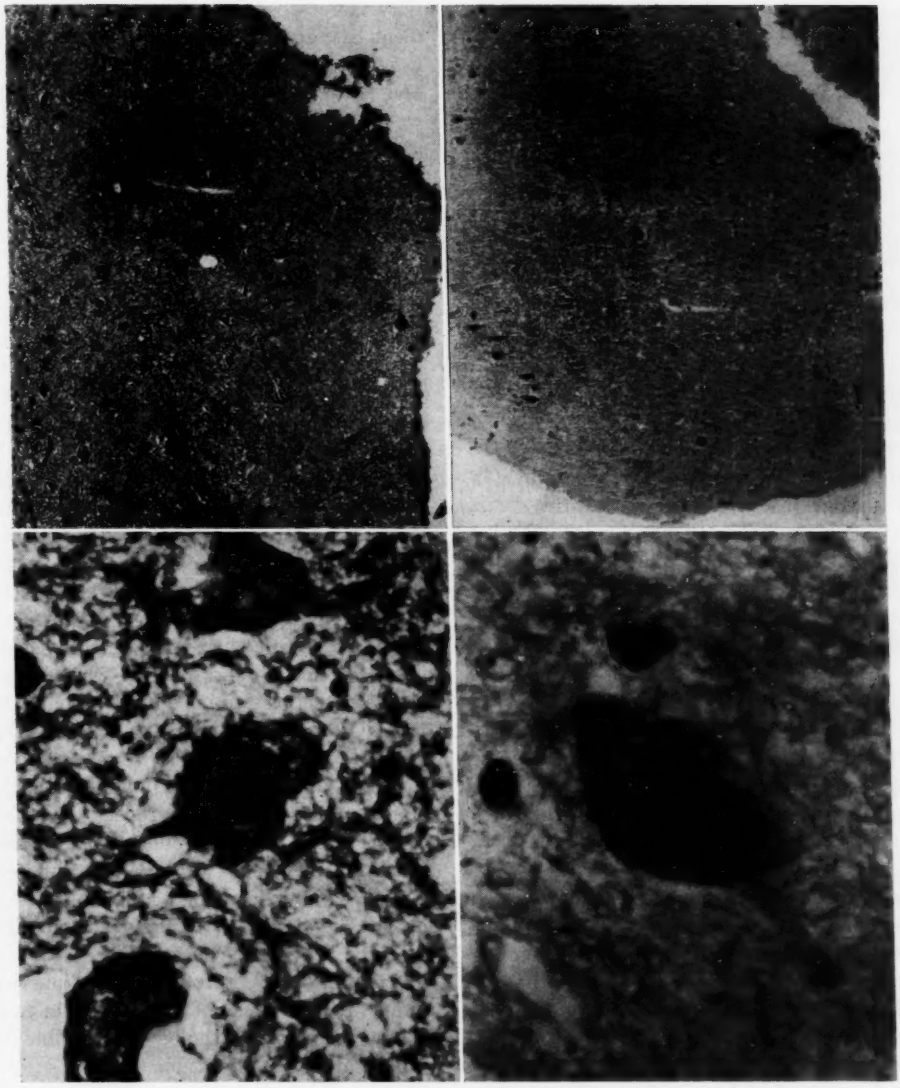

FIG. 2. (a) Biopsy specimens of thalamus; photomicrographs ×105 (H & E). (b) Neurons from ventro-lateral thalamus; ×1750 (H & E).

Evidence of autonomic dysfunction in many Parkinsonian patients, moreover, suggests hypothalamic involvement which may be related to third ventricular dilatation. This was demonstrated by pneumoencephalography in 18 of the 20 Parkinsonian patients in this series and all of our patients with birth injuries, but none of those with dystonia. Although the presence of third ventricular dilatation did not preclude excellent permanent improvement in 12 of these patients (six months to two and one-half year

TABLE 1
Summary of Clinical Localization and Biopsy Confirmation

Clinical Localization	Biopsy Confirmation			
	Globus Pallidus	Thalamus	Probable Globus Pallidus (inadequate tissue)	Cerebral White Matter
Globus Pallidus	17	0	6	0
Thalamus	0	6	0	0
Medial Margin G. P. (Dilated 3rd Ventricle)	0	0	0	2
Internal Capsule	0	0	0	3

follow-up) as to tremor and rigidity, none of this group maintained lasting benefit with respect to an expansion of his daily activities. The four patients in this series (two with Parkinsonism and two with dystonia) who have maintained improvement both as to tremor and rigidity and also daily activities, all had roentgenographically normal third ventricles (*i.e.*, less than 8 mm in lateral dimension).

CONCLUSIONS

These studies suggest that there is a fixed (6 per cent) inherent error in the pneumotaxic method as applied to human surgery, probably reflecting a variability of intracerebral structures, and a 10 per cent operational error in our own modification which can further be reduced. Morbidity accompanying these operations is closely related to these inherent and operational errors.

One may infer from these data that destruction of a critical volume of globus pallidus (including fibers of the ansa lenticularis) and the nucleus ventralis-lateralis thalamicus abolishes rigidity and attenuates or abolishes tremor. Disappointments in the long-term alleviation of Parkinsonism as contrasted with more lasting general improvement in patients having pure dyskinesias may be a reflection of the protean nature of Parkinson's Disease.

Objective improvement followed 32 of our 34 operations in 28 patients. Although we may therefore quote a 94 per cent improvement rate for this operation, the object relief of tremor and rigidity has been dramatic and permanent in only 60 per cent of our cases. Moreover, only four patients in this group are still gainfully employed, although seven others continue to claim subjective improvement up to two and one half years following their surgery.

SUMMARY

Biopsy specimens have been obtained and studied during 34 stereotaxic operations for Parkinsonism and dyskinesias. Accurate clinical localization was proved in 23 cases by positive identification of cells of the globus pallidus in 17 and the thalamus in six cases. Six of the specimens were of sufficiently poor quality to make positive identification questionable, but these appeared to be from the globus pallidus. Five "negative" biopsies showed cerebral white matter only.

By correlation with our clinical method of localization we find that 26 (74 per cent) proved to be accurately placed lesions, and three (10 per cent) were of questionable accuracy. In addition, there were three questionable specimens which, judging from the clinical results, probably reflect operative errors. There were two negative biopsies, which must be relegated to errors inherent in the stereotaxic method reflecting pathological distortion of landmarks, notably the third ventricle.

Symptoms of autonomic dysfunction found in some cases of Parkinsonism may be associated with pathology responsible for third ventricular dilatation.

REFERENCES

1. Bertrand, C. A pneumotaxic technique for producing localized cerebral lesions and its use in the treatment of Parkinson's disease. J. Neurosurg., **15**: 251–264, 1958.
2. Carpenter, M. D. and Whittier, J. R. Study of methods for producing experimental lesions of the central nervous system with special reference to stereotaxic technique. J. Comp. Neurol., **97**: 73–131, 1952.
3. Denny-Brown, D. Diseases of the basal ganglia

and subthalamic nuclei. In *Oxford Loose-Leaf Medicine*, p. 284. Oxford Univ. Press, New York, 1946.

4. Horsley, V. and Clarke, R. H. The structure and functions of the cerebellum examined by a new method. Brain, **31**: 45–124, 1908.
5. Housepian, E. M. A biplane grid utilizing a common horizontal plane for localization of radiographic landmarks in two conventional roentgen views. Radiology, **70**: 398–400, 1958.
6. Housepian, E. M. Discussion of paper by W. J. Fry et al. Tr. Am. Neurol. A., **83**: 19–20, 1958.
7. Housepian, E. M. and Carpenter, M. D. Spatial relationships between the globus pallidus and the anterior commissure. J. Neurosurg., **14**: 363–373, 1957.
8. Housepian, E. M. and Pool, J. L. An evaluation of pallido-ansal surgery: Hypokinesia as a primary symptom of Parkinsonism. In *Pathogenesis and Treatment of Parkinsonism*, Fields, W. S., ed. Thomas, Springfield, Ill., 1958.
9. Schaltenbrand, G. and Nurnberger, S. Radiographic landmarks for stereotaxic operations. In Schaltenbrand, G. and Bailey, P. *Introduction to Stereotaxis with an Atlas of the Human Brain*, Vol. 1, p. 421. Grune & Stratton, New York, 1959.
10. Spiegel, E. A. Tonus. In *Handbuch der normalen und pathologischen Physiologie*., Bethe, A., ed., Vol. 9, pp. 711–740. Springer, Berlin, 1929.
11. Spiegel, E. A. *Tonus des Skelettmuskulatur*. Springer, Berlin, 1927.
12. Spiegel, E. A. and Bernis, W. J. Die Zentren der statischen Innervation und ihre Beeinflussing durch Klein-und Grosshirn. Arbeiten Nurol., Inst., Wiener Univ., **27**: 197–224, 1925.
13. Spiegel, E. A. and Wycis, H. T. Pallidoansotomy: Anatomic-physiologic foundation and histopathologic control. In *Pathogenesis and Treatment of Parkinsonism*, Fields, W. S., ed., Chap. 3, pp. 87–91. Thomas, Springfield, Ill., 1958.
14. Spiegel, E. A. and Wycis, H. T. Pallidothalamotomy in chorea. Arch. Neurol. & Psychiat., **64**: 295–296, 1950.
15. Spiegel, E. A. and Wycis, H. T. *Stereoencephalotomy. Part I. Methods and Stereotaxic Atlas of Human Brain*. Grune & Stratton, New York, 1952.
16. Spiegel, E. A., Kletzkin, M. and Szekely, E. G. Pain reactions upon stimulation of the tectum mesencephali. J. Neuropath. & Exper. Neurol., **13**: 212–220, 1954.
17. Spiegel, E. A., Wycis, H. T. and Freed, H. Stereoencephalotomy, thalamotomy and related procedures. J. A. M. A., **148**: 446–451, 1952.
18. Spiegel, E. A., Wycis, H. T., Baird, H. W. and Szekely, E. G. Functional state of basal ganglia in extrapyramidal and convulsive disorders. A.M.A. Arch. Neurol. & Psychiat., **75**: 167–174, 1956.
19. Spiegel, E. A., Wycis, H. T., Marks, M. and Lee, A. J. Stereotaxic apparatus for operations on the human brain. Science, **106**: 349–350, 1947.
20. Talairach, J., David, M., Tournoux, D., Corredor, H. and Kvasina, T. *Atlas d'anatomie stereotaxique*. Masson, Paris, 1957.
21. Wycis, H. T. and Spiegel, E. A. Ansotomy in paralysis agitans. Confinia neurol., **12**: 245–246, 1952.
22. Wycis, H. T. and Spiegel, E. A. Thalamotomy and mesencephalothalamotomy: Neurosurgical aspects (including treatment of pain). New York State J. Med., **49**: 2275–2277, 1949.
23. Wycis, H. T., Szekely, E. G. and Spiegel, E. A. Tremor on stimulation of the midbrain tegmentum after degeneration of the brachium conjunctivum. J. Neuropath. & Exper. Neurol., **16**: 79–84, 1957.

EVOKED POTENTIALS FROM THE EXPOSED SOMATO-SENSORY CORTEX IN MAN

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We are pleased to have this opportunity to pay tribute to Professor Spiegel, who has devoted his life to an impressive series of experimental studies of brain function in animals and in man. One of his greatest distinctions has been the application of knowledge and experimental methods of the animal laboratory to the solution of clinical neurological problems. Equally important has been his ability to make use of clinical data to elucidate important general principles of brain function. We present this study of evoked potentials from the exposed human cerebral cortex obtained during operations under local or general anesthesia, carried out for the treatment of focal epilepsy, as a contribution to the general field of experimental neurology, the field of Doctor Spiegel's main interest and scientific work.

The technique of recording evoked potentials has contributed much to our knowledge of functional localization in the brain of many experimental animals, but it has received only very limited application to studies of the human brain. Woolsey and Erickson (9) described very briefly some preliminary results of recording evoked potentials from the exposed somato-sensory cortex in man under deep anesthesia. The points localized by evoked potentials were said to correspond well with those determined by subjective reports of the patient to local electrical stimulation carried out before general anesthesia. In a discussion of this brief note, Walker (10) reported similar observations, but we are not aware of any complete published report of these findings. The use of an ink-writing oscillograph made uncertain the true form and latency of the evoked potentials obtained.

Recording through the unopened skull from electrodes placed on the scalp, presumably in the vicinity of the post-central gyrus in man, Dawson (1–3) was able to detect evoked potentials of about 2–3 microvolts in amplitude in response to ulnar nerve stimulation. This was done by a summation technique which brought them out of the background "noise" which makes them invisible in the usual records taken from the scalp surface. The latency of these potentials in man was 22–23 msec. following shocks to the ulnar nerve at the wrist, and about 18 msec. when stimulating at the elbow. The time consumed in obtaining such records would make this method quite impractical for use during surgical procedures. In fact, it may be that the tedious and time-consuming nature of all evoked potential methods as usually employed may explain why we do not have more data on evoked potentials from the exposed cortex in man.

In the present report we will describe a technique for obtaining evoked potentials by means of a multi-beam cathode ray oscilloscope, which makes it possible to locate a sensory area rather quickly in the exposed human brain using either local or general anesthesia. Preliminary results of the comparison between localization by evoked potentials and by stimulating the same points in conscious patients will be presented.

TECHNIQUE

In order to simplify the method in these preliminary studies, electrical stimulation

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of the ulnar nerve at the elbow has been used, rather than cutaneous stimulation, to study the localization and form of the evoked potentials from the exposed somato-sensory cortex.

After exposure of the cortex in the usual manner for operations on patients with focal epilepsy (7, 8) using local anesthesia, the central fissure was identified by electrical stimulation of a few points on the pre- and post-central gyri. Eight recording electrodes were then distributed in orderly arrays on the cortical surface. These were chlorided silver balls about 1.5 mm. in diameter, held in an adjustable holder. Each electrode was individually adjustable in all directions by its attachment to a stainless steel tube passed through a ball and socket joint attached to a bar upon which was mounted the entire assembly. This was clamped through a universal joint to the edge of the skull at the border of the craniotomy opening. The clamp holding the assembly to the skull also served as the reference electrode for unipolar recording of evoked potentials from the eight electrodes. More recently, a small rod screwed into the skull has been substituted for the clamp.

The eight electrodes were connected to a selector switch which made it possible to connect quickly four electrodes at a time to a 4-channel amplifier oscilloscope apparatus. This apparatus consisted of four Tektronix preamplifiers and a 4-beam cathode-ray oscilloscope mounted on a mobile table, as shown in Figure 1. Single sweeps of the four beams of the oscilloscope were photographed by means of a Grass camera. The sweeps were triggered by a Grass stimulator, which provided 0.1 msec. pulses for stimulation of the ulnar nerve through the skin at the elbow. Intensity of nerve stimulation was adjusted so that the patient felt a slight pricking sensation in the ulnar distribution of the hand, sometimes associated with minimal twitching movements of the arm or hand muscles. Shocks were administered at the rate of 1/sec. There was no sensation of pain with the brief shock used at intensities just above the threshold for tactile sensation.

The time constant of the recording amplifiers was adjusted to attenuate all frequencies below 80 per second in some of the records, in order to eliminate from the record the slow waves of spontaneous cortical activity and the slower components of the evoked potentials. This made the more rapid primary components of the evoked potentials more easily visible at the amplification necessary to see them clearly. A longer time constant permitting records of frequencies down to 8 per second was also employed when studying the later, more prolonged components of the evoked potention complex.

RESULTS

Cortical evoked potentials in response to contralateral ulnar nerve stimulation have been recorded in 11 adult patients during exposure of the cortex for the treatment of temporal lobe seizures. In all, the epileptic process appeared to be confined to the temporal lobe, so that the evoked potentials from the arm area of the post-central gyrus may be considered fairly normal. In seven of these patients, all records were taken when they were fully conscious without general anesthesia. In the remaining four patients, records were taken while the patients were under light pentothal and nitrous oxide anesthesia.

COMPONENTS OF THE EVOKED POTENTIAL COMPLEX

Evoked potentials were easily seen in single trace oscillographs taken with unipolar electrodes from the hand or arm area of the post-central gyrus in all patients, with or without general anesthesia.

The initial rapid component of the evoked potential complex in the unanesthetized cortex consisted of a small surface positive deflection, not more than 50 to 100 microvolts in amplitude, which followed the

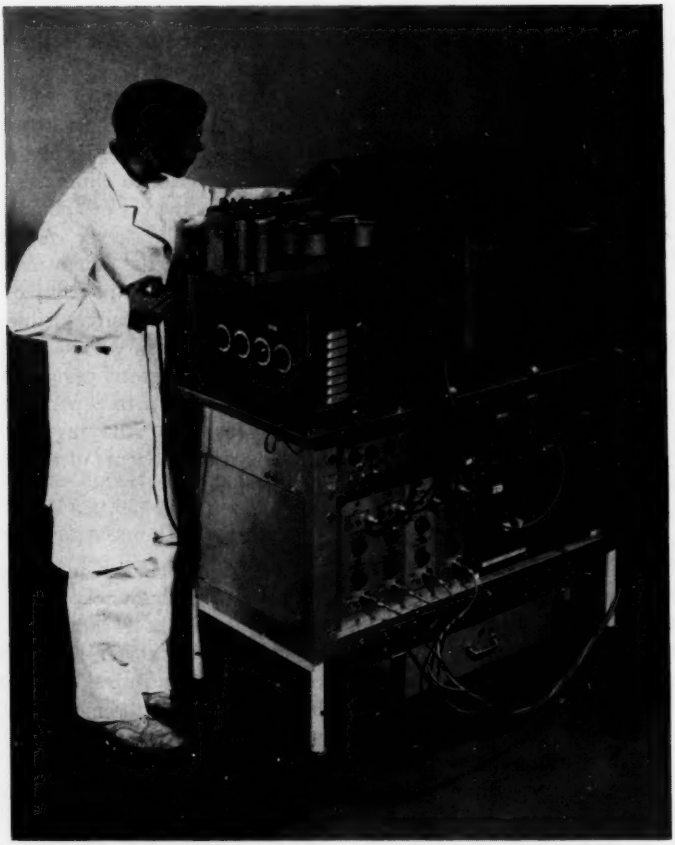

FIG. 1. Apparatus assembled on a mobile cart for recording evoked potentials in the operating theater. A 4-beam cathode ray oscilloscope is mounted on top with a Grass camera for photographing the traces. Beneath the Grass camera is shown the Grass stimulator and below, four Tektronix amplifiers. Other components shown represent those used for microelectrode recording and do not concern the present study.

shock to the ulnar nerve at the elbow, with a latency of about 18 msec., with a narrow range of variation from 16 to 20 msec. in different subjects. This initial rapid complex was usually diphasic, or triphasic, the peak latencies of the three initial responses being about 20, 22 and 24 msec. respectively, as shown in the sample records of Figure 2. This initial complex was followed by larger slow wave responses, reaching 200 to 500 microvolts in amplitude. The first of these late responses usually was surface negative with a peak latency of about 50 msec. It was followed by a slow surface positive wave with a peak latency of about 100 msec. Additional slow waves were sometimes seen as well, but were not included in this study because of their extreme variability. In fact, all of the slow late responses showed much variability, as illustrated in the successive sweeps of Figures 3 and 4, while the initial rapid complex was quite stable.

Since the interest of the present study was particularly in localization, rather than in an analysis of all components of the

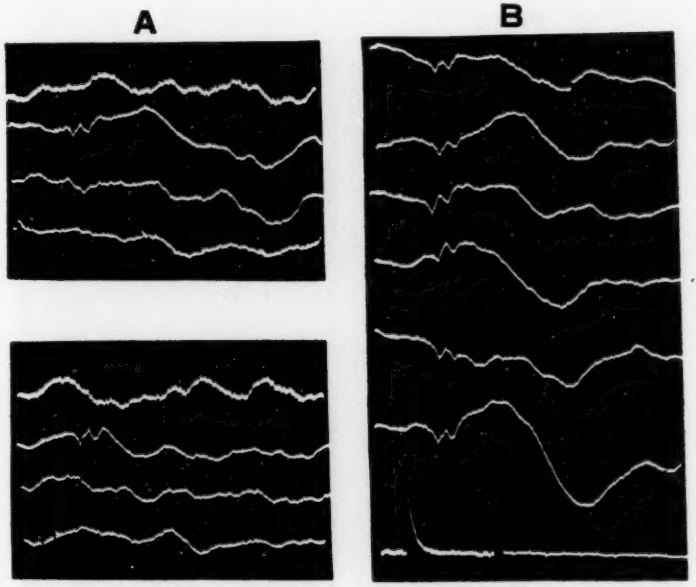

FIG. 2. Sample tracings of response from the post-central gyrus to contralateral ulnar nerve stimulation. The shock artifact appears at the beginning of each sweep. On the left (A) is shown single sweeps of the four beams of the oscilloscope recording from four electrodes along the post-central gyrus 1 cm. apart. These are two successive sweeps. It will be noted that in the second line of each sample a clear evoked potential is seen while none appear in adjacent lines. (Short time constant amplifier used as described in text.)

To the right (B) is shown a series of six sweeps from the same point of maximum evoked potential response to illustrate the variability with successive ulnar nerve stimuli. Note that the primary complex is quite stable with a latency of about 18 msec. and composed of three waves, as described in the text. The following slow later components of the evoked potential response are best shown in the lower sample of these successive traces. It will be noted that these slow components are highly variable, as compared to the constancy of the primary complex. Calibration lines at the bottom indicate the response to a square wave 100/^{n}v signal on the left and time indications of 10 msec. to the right.

evoked potential complex, the spontaneous waves and the slow components of the evoked potentials were attenuated by limiting the low frequency response of the amplifiers to 80 cycles per second. This resulted in a very stable initial rapid response, not confused by the variable slow waves, as illustrated in a series of successive sweeps shown in Figure 3B.[3]

The initial rapid complex of the response appeared about the same with patients under light pentothal and nitrous oxide anesthesia. Changes in the late components with anesthesia were hard to evaluate because of their extreme variability.

[3] The slow late responses are under study at present and will be the subject of a later report. They seem to correspond roughly with the late components of evoked potentials recorded from unanesthetized animals as described by Galambos (4).

LOCALIZATION

Only the initial rapid phase of the evoked potentials will be considered in localization studies, since it was most stable in localization as well as in amplitude. In Figure 2A it is shown to appear in only one of four traces simultaneously recorded from electrodes 1 cm. apart arranged from above downward on the post-central gyrus.

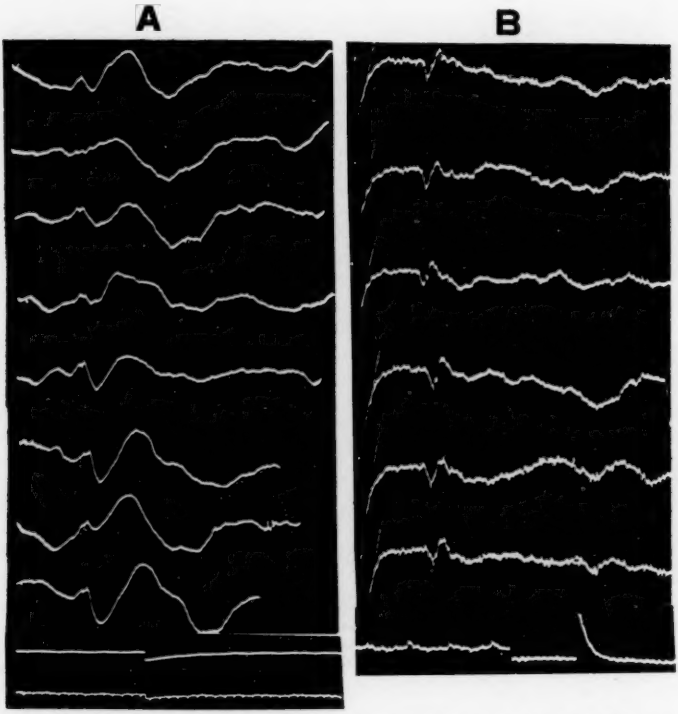

FIG. 3. Illustrations of successive sweeps of responses from a single point on the post-central gyrus recorded in A with the amplifier set to record frequencies above 8 cycles/second, while in B the amplifier is increased in gain and set to limit the low frequency responses to 80 cycles/second. Note the highly variable complex slow components of the response in A as compared to the constant primary complex in the series shown at B. Calibration 100 microvolts. Time line 10 msec.

In order to survey the distribution of potentials as rapidly as possible, the initial series of eight electrodes was arranged in a line from above downwards on the post-central gyrus, covering the area both above and below the presumed location of the arm and hand representation, as illustrated in Figure 4A (pt. M.S., see also Figure 7). Electrodes were spaced 1 cm. apart for the initial records, and then brought closer together when more refined localization was desired. After the electrodes from which maximum responses were obtained were identified, a second line of eight electrodes was placed at right angles to the first, crossing the pre-central and post-central gyri in a longitudinal direction, as shown in Figure 4B. Then, in some cases, vertical and horizontal lines of more closely spaced points were used to make more precise the distribution of potentials both in the sagittal and coronal planes.

After the evoked potentials had been recorded, the electrodes were left in place and stimulated electrically to determine the sensory responses from the same points used in recording the evoked potentials. Additional points were stimulated as well in most cases. The distribution of evoked potentials and sensory responses to stimulation in three patients are shown in Figures 5, 6 and 7.

A schematic representation of the location of points on the exposed cortex of pa-

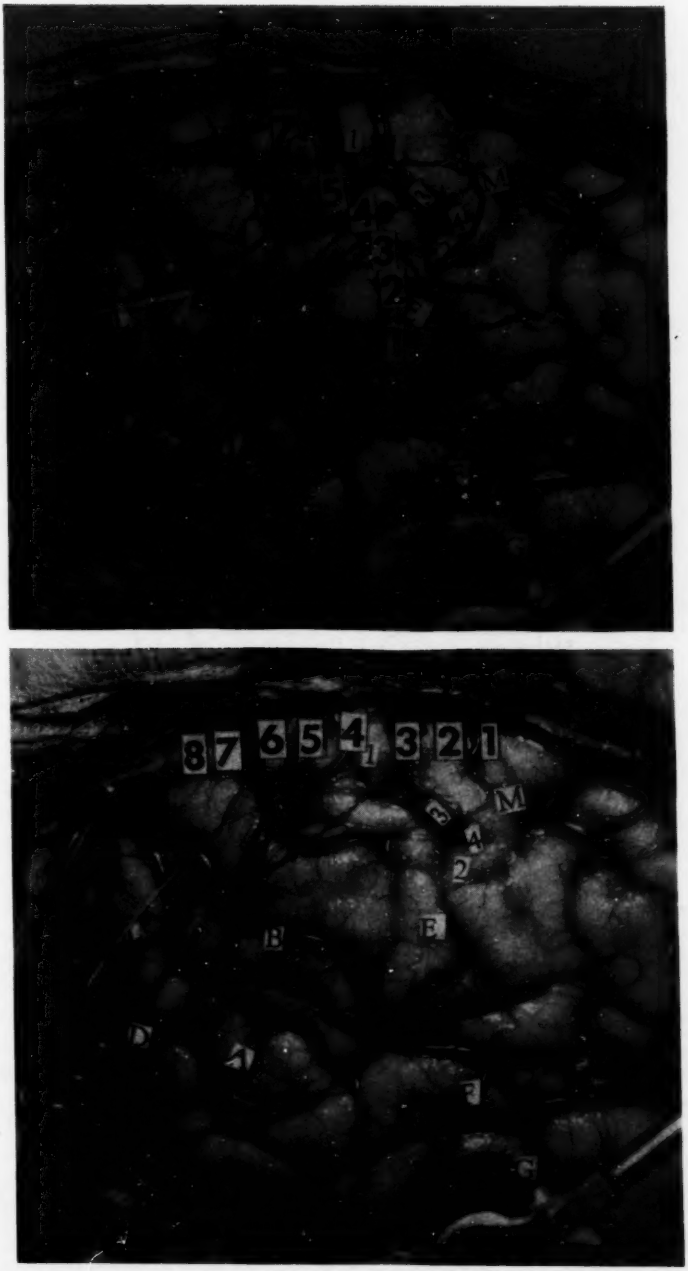

FIG. 4. Photographs of the exposed cortex, the right hemisphere, (pt. M.S.), showing in the upper photograph arrangements of recording electrodes in a line along the post-central gyrus from below upward, eight electrodes being placed simultaneously. Following recording from this line electrodes were re-arranged in an anterior-posterior line across the post-central gyrus, as shown in the photograph below.

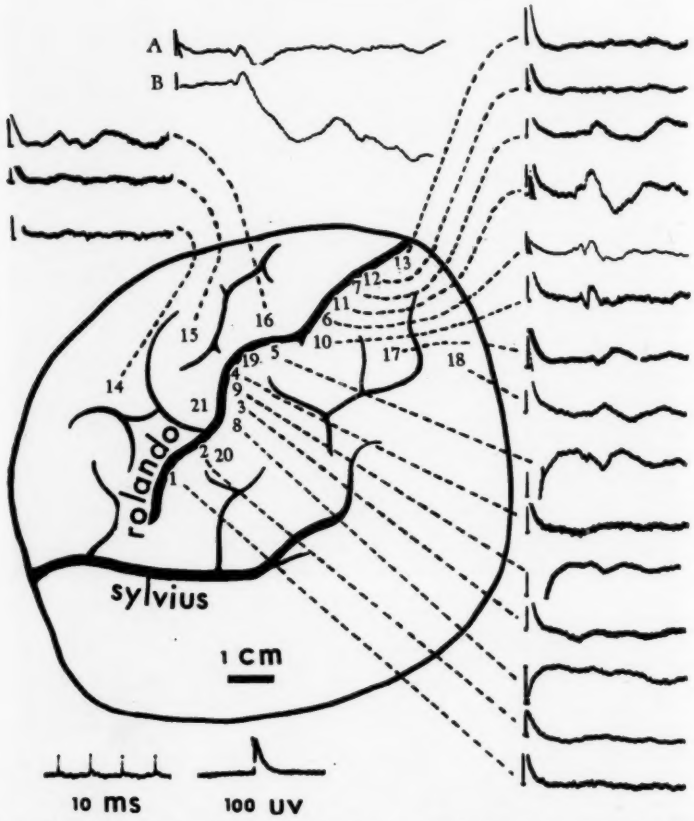

FIG. 5. Cortical evoked potentials in response to contralateral ulnar nerve stimulation (pt. A.M.) Left central and temporal regions as exposed at operation under local anesthesia. Numbers refer to points of recording, stimulation or both. A and B: recordings from point 6 at low frequency response settings of 8 and 80 cycles/second respectively. Stimulation artifact is at the beginning of each trace. The following table lists the cortical point, time of stimulation, voltage and responses.

Point	Time	Voltage	Response
19	12.14	2 volts	Sensation of worms in right thumb, index and middle fingers.
20	12.16	2 volts	Sensation in right lower lip and movement of lip.
21	12.20	2 volts	Counting arrested.
8	12.34	2 volts	Numbness right thumb.
9	12.35	2 volts	Numbness in right thumb and index finger.
5	12.36	2 volts	Numbness in right index, middle and ring fingers; no sensation in little finger.
10	12.37	2 volts	Numbness; whole hand.
11	12.38	2 volts	Numbness from fingers to elbow, including whole arm.
12	12.39	2 volts	Numbness; top forearm and upper arm.
13	12.40	3 volts	Numbness below right shoulder.
16	12.46	3 volts	Extension of two fingers; sensation of hand stiffening.
15	12.47	3 volts	Sensation of heat down right arm.

tient A.M. is shown in Figure 5. The line around the central figure represents the craniotomy opening. The fissures of Sylvius and Rolando are indicated by dark lines. This was traced from a life-size photograph taken with the electrodes in place at the time of operation and with tickets placed on the cortex in the manner customary for these operations, as described by Penfield and Erickson (6) and Penfield and Rasmussen (7). Oscilloscope tracings are shown as they were obtained from each of the numbered points connected with the dotted lines. Numbers indicate positive responses to electrical stimulation only, points where no response was obtained are not shown.

It is to be noted in Figure 5 that the maximum primary cortical evoked potentials were obtained from #6 and 10 in the post-central gyrus. Longer latency and slower responses were obtained from a few points above and below this area, and from one point on the pre-central gyrus (#16) across from points 6 and 10 on the post-central gyrus.

Sensory responses to electrical stimulation of these two points of maximum evoked potential response showed for point 10 there was numbness of the whole hand, not restricted to the ulnar nerve distribution. The adjacent point 5, from which a slow wave response was obtained, with only a very small primary complex, produced numbness in the index, middle and ring fingers. The point above, at #11, where a slow wave response also was obtained, produced numbness from the fingers to the elbow stated to include the whole arm. It is obvious that although these sensory responses were limited to the hand and arm, or to the hand only when stimulating within the area of maximum primary response, they did not confine themselves solely to the ulnar nerve distribution.

The remainder of the sensory responses are given in the legend to this figure.

Another example is given in Figure 6, showing the distribution of evoked potentials schematically in patient J.C. In this case it is noted that the maximum primary responses were obtained from points 5 and 14, with a smaller primary response posterior to 14 at point 6. In this instance, sensory responses to electrical stimulation were confined to the ulnar distribution of the hand. At point 5, which was very near the pre-central sulcus, there was a feeling of numbness in the ulnar side of the left hand, together with flexion of the little finger, a sensory and motor response. At point 14, stimulation produced a sensation of numbness in the ulnar side of the left hand. At point 16, there was numbness in the left forearm, more noticeable at the elbow. Below, to the right of this figure, are shown sample responses from point 14, recorded first with the short time constant amplifier in A and then with the longer time constant amplifier in B, to show the large secondary slow wave response which follows the primary complex when it is not attenuated by the amplifiers.

A third example is shown in Figure 7, representing the results obtained from patient M.S., with the right central and Sylvian regions exposed at operation under general anesthesia with pentothal and nitrous oxide. This was a relatively light level of anesthesia at the time of the evoked potential recording and electrical stimulation of the pre-central gyrus.

Responses to contralateral ulnar nerve stimulation appeared most marked in this patient from points 14, 15 and 18 lying along the upper border of the craniotomy. Exploration was incomplete in this case, because of the limited exposure of the upper portion of the post-central region, but it was presumed that the post-central gyrus must turn backwards along the border of the fissure in view of these results obtained, though this could not be proven. A small response was also obtained from points 8 and 13 extending up to the pre-central sulcus. Relation to sensory responses to stimulation could not be made, of course, due to the general anesthesia.

At the bottom of this figure is shown

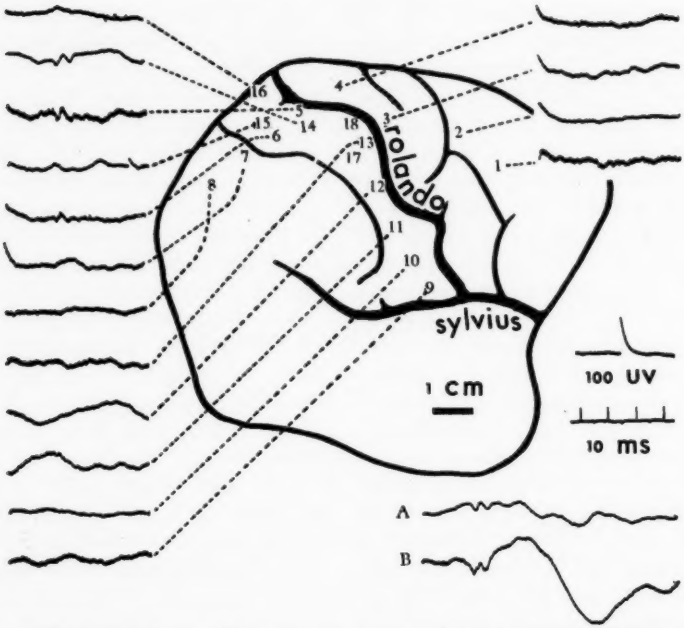

FIG. 6. Cortical evoked potentials in response to contralateral ulnar nerve stimulation (pt. J.C.) Right central and temporal regions as exposed at operation under local anesthesia. Numbers refer to points of recording, stimulation or both. A and B: recordings from point 14 at low frequency response settings of 8 and 80 cycles/second respectively. Stimulation occurred at the beginning of each trace. The following table lists the cortical point, time of stimulation, voltage and response.

Point	Time	Voltage	Response
17	12.00	1 volt	Slight vibration of whole left arm.
18	12.02	1 volt	Tingling; left index finger.
15	12.12	1½ volts	Numbness; whole left arm.
13	12.20	1½ volts	Numbness; all left fingers and forearm.
14	12.22	1½ volts	Numbness; ulnar side, left hand.
11	12.25	2 volts	Numbness in mouth, center lower jaw and teeth.
16	12.27	2 volts	Numbness; left forearm, more noticeable at elbow.
4	12.32	2 volts	Slight numbness, left hand, going up arm.
5	12.34	2 volts	Numbness; ulnar side left hand, and flexion little finger.
6	12.36	2 volts	Numbness; left little finger and slightly in ring finger; slight movement both fingers.

again the comparison between the responses with the long time constant amplifier in A and the short time constant amplifier in B. Comparison with tracings A and B in Fig. 6 indicates a marked similarity of both the primary complex and the large later secondary slow wave responses under local and general anesthesia. Comparing this record with others taken under general anesthesia, it seemed obvious that the primary evoked potential complex was as readily identified without anesthesia as with anesthesia, when recorded in this manner. In general, the level of background activity was somewhat reduced by the deeper levels of anesthesia, but no obvious

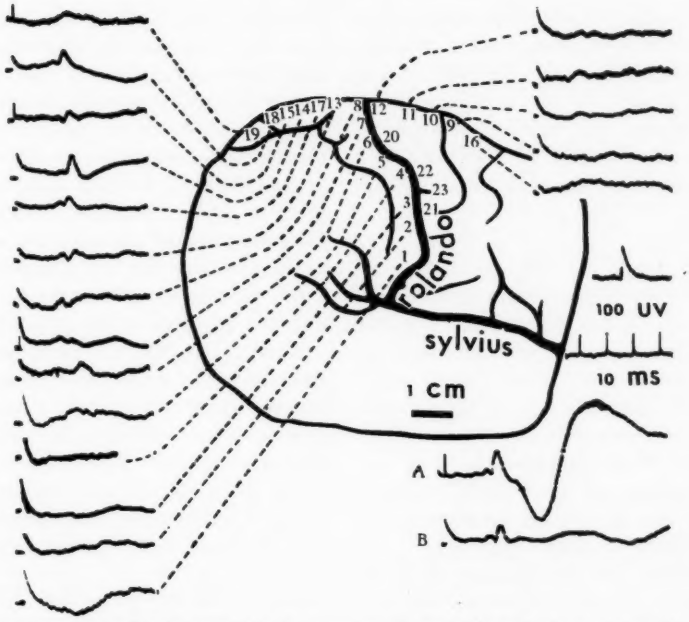

FIG. 7. Cortical evoked potentials in response to contralateral ulnar nerve stimulation (pt. M.S.) Right central and temporal regions are exposed at operation under general anesthesia. Numbers refer to points of recording, stimulation or both. A and B: recordings from point 14 at low frequency responses settings of 8 and 80 cycles/second respectively. Stimulation occurred at the beginning of each trace. The following table lists the cortical point, time of stimulation, voltage and response.

Point	Time	Voltage	Response
20	12.05	3 volts	Coughed and had short seizure consisting of twitching of left face and neck.
21	12.10	4 volts	Opening and trembling of jaw and retraction of left cheek.
22	12.12	4 volts	Opening and trembling of jaw and retraction of lip.
23	12.16	5 volts	Jaw and cheek pulled toward left.

All of the above responses continued several seconds after stimulation. The Rolandic sulcus probably turns posteriorly above the exposure.

change took place in the amplitude or form of the primary evoked potential complex, as recorded in these experiments.

There was some evoked potential response from the pre-central gyrus adjacent to the area of maximum response from the post-central gyrus, but responses were usually of lower voltage and not as constant. The latency, however, seemed to be the same from the pre-central gyrus as from the post-central gyrus.

In summary, there were six patients in whom electrical stimulation gave satisfactory sensory responses from the central portion of the evoked potential area to stimulation of the contralateral ulnar nerve. In these six cases, the sensory responses were as follows: tingling in the ring finger, tingling in all fingers of the hand, numbness ulnar side of hand and flexion of little finger, numbness of fingers and arm to elbow, a feeling in the ring and middle finger,

electricity feeling in the ring and middle finger with some clonic movement. Sensory responses obtained from the post-central gyrus just below the area of maximum evoked potential localization yielded responses in other fingers of the hand and thumb, obviously adjacent to the ulnar distribution.

DISCUSSION

By the use of a four-beam oscilloscope and a selective switch making possible rapid shift from one set of four recording electrodes to another, there being eight electrodes placed at one time on the exposed cortex, it is possible in a limited period of time, (about 15–30 minutes) to map out the distribution of maximum primary evoked potential in the post-central gyrus during a routine surgical procedure. This is made possible by attenuating the large rhythmic slow background activity and the slow wave components of the evoked potential, which are highly variable, bringing out more clearly the more rapid primary complex which is of very low voltage and sometimes masked by the spontaneous activity and slow components of the evoked response. These slow components deserve special study in and for themselves, since they seem to be related to the attentive factors in sensory perception as suggested by Galambos (4), but due to their high variability and greater extent in localization, they do not provide a stable basis for localization studies. The primary complex seems very stable, either with or without anesthesia, and is restricted to a cortical area consistent with the sensory responses to stimulation.

Precise correlation was not obtained between the ulnar distribution of sensory responses and those obtained through cortical stimulation, which tended to extend somewhat beyond the sensory distribution of the ulnar nerve in some cases. Considering the possibility of some spread of current during stimulation, this result is perhaps not surprising. No sensory responses were obtained, however, which could not be considered restricted to the immediately adjacent sensory representation such as the median distribution of the hand adjacent to that of the ulnar distribution.

Considering the brief time required for such an evoked potential localization, this technique would seem to be of practical importance for use in neurosurgery, especially when subjective responses to stimulation are uncertain or impossible to obtain.

Now that a suitable technique has been established, we intend to continue our studies to complete the map of both primary and secondary somatic sensory cortex in man, together with correlations with stimulation results. Studies of the significance of the later slower potential components of the response are also being undertaken.

SUMMARY AND CONCLUSIONS

A technique has been described for rapid recording and localization of evoked potentials from the exposed cerebral cortex in man, with or without anesthesia. It consists essentially in the use of a 4-beam oscilloscope and a switch to select rapidly successive sets of four recording electrodes. The primary evoked potential complex is then brought out more clearly from the slower later responses, as well as from the spontaneous rhythms of the cortex by limitation of the low frequency response characteristics of the recording amplifiers. The distribution of cortical responses to electrical stimulation of the ulnar nerve was then compared with subjective sensory responses determined in seven patients, and to electrical stimulation of the same cortical points. The distribution of evoked potentials alone was studied in an additional four patients operated upon under general anesthesia.

The initial rapid evoked potential complex of 50 to 100 microvolts in amplitude followed a shock to the ulnar nerve at the elbow with a latency of about 18 msec. The

primary complexes were highly stable in amplitude and location in patients with or without anesthesia. The later slow components of the evoked potentials followed ulnar nerve shock by 50 to 100, or even 300 msec., but these waves were highly variable and not so well localized as were the shorter latency primary responses.

Considering only the localization of the primary complex, the cortical area from which these appeared with maximum voltage yielded only sensory responses in the contralateral hand and arm when electrically stimulated. In some patients these sensations were confined to the ulnar distribution of the hand, while in others some extension into the median distribution of the hand was obtained.

These preliminary observations support the assumption that cortical localization of sensory areas by the evoked potential method bears a close correspondence to the localization obtained in conscious human subjects by local electrical stimulation. The physiological significance of the more extensive distribution of the slower components of the evoked potential complex is uncertain.

REFERENCES

1. Dawson, G. D. Cerebral responses to electrical stimulation of peripheral nerve in man. J. Neurol. Neurosurg. & Psychiat., **10:** 137–140, 1947.
2. Dawson, G. D. Cerebral responses to nerve stimulation in man. Brit. M. Bull., **6:** 326–329, 1950.
3. Dawson, G. D. A summation technique for the detection of small evoked potentials. EEG. Clin. Neurophysiol. **6:** 65–84, 1954.
4. Galambos, R. Electrical correlates of conditioned learning. In *The Central Nervous System and Behavior*, Brazier, M. A. B., ed. Josiah Macy, Jr., Foundation, New York, 1958.
5. Hernandez-Peon, R. and Donoso, C. M. Subcortical photically evoked electric activity in the human waking brain. (Free communication 20)
6. Penfield, W. and Erickson, T. C. *Epilepsy and Cerebral Localization*, p. 623. Thomas, Springfield, Ill., 1941.
7. Penfield, W. and Jasper, H. *Epilepsy and the Functional Anatomy of the Human Brain*, p. 896. Little, Brown, Boston, 1954.
8. Penfield, W. and Rasmussen, T. *The Cerebral Cortex of Man*, p. 248. Macmillan, New York, 1950.
9. Woolsey, C. N. and Erickson, T. C. Study of the postcentral gyrus of man by the evoked potential technique. Tr. Am. Neurol. A., **75:** 50–52, 1950.
10. Woolsey, C. N., Walker, A. E. and Erickson, T. C. Somatic afferent representation in the cerebral cortex of man. 4th International Neurological Congress, Paris, 1949.

BILATERAL THALAMOTOMY IN PARKINSONISM

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There is no doubt that an accurately placed lesion of sufficient size in the region of the ventrolateral nucleus of the thalamus produces complete and enduring relief of parkinsonian tremor and rigidity, but the question about the bilateral thalamotomy is still open for discussion. Hassler and Riechert (2) have been the first to report cases with states of impaired consciousness, confusion and amnesia in which bilateral thalamic operation has been performed. For this reason they have advocated the combination of pallidotomy on one side and thalamotomy on the other side. This opinion is also shared by Walker (4) and by Spiegel (3), who discusses the possibility of producing a leucotomy effect because one cuts the thalamo-cortical pathway by a lesion in the area of the nucleus ventralis anterior of the thalamus. Cooper (1), however, has not seen a lobotomy effect, but most of his thalamic lesions have been unilateral. In their series of more than 600 cases, Cooper and Bravo (1) have performed bilateral operations for bilateral parkinsonism in slightly more than 50 cases, but most of the bilateral cases have had the pallidal operation on one side and the thalamic on the other. Therefore the question about the bilateral operation on the thalamus cannot yet be answered definitely. But the feeling of Cooper (1) has been that he would be hesitant to sacrifice the same structure bilaterally, no matter what the structure was.

In our own series of 225 operations on 187 cases, bilateral operations have been performed on 38 patients. As candidates for bilateral operation, only those cases who have tolerated the initial operation without complications and who have enjoyed an excellent result from the operation for the first side, have been selected. The bilateral operation was usually carried out with an interval of six months or more between the left-sided and the right-sided procedure. Of these 38 patients, six cases have had bilateral thalamic operations with unipolar coagulation of the ventrolateral nucleus of the thalamus (*i.e.* nucleus ventralis oralis posterior, v.o.p. of Hassler (2). It is the purpose of this report to give a full account of the operative results of these cases. As method of lesion production the Riechert (2) instrument for introduction of the electrode and the Wyss (5) apparatus for electrocoagulation is used. With the high frequency apparatus of Wyss (5) and with specially-constructed unipolar electrodes, lesions the size of 200–250 cmm. are made. In our experience these lesions performed with one to three electrocoagulations are large enough to give consistent and complete relief of tremor and rigidity.

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CASE REPORTS

Case 1. G.A., a woman aged 68, had suffered from tremor and muscular rigidity, first on the right and later on the left side for three years.

Neurological examination showed bilateral tremor and rigidity of all extremities, more marked on the right side than on the left. The gait was stiff and the patient did not swing her arms in walking. Her speech and her writing, however, did not show any abnormality. The encephalogram showed a slight enlargement of both lateral ventricles.

Operation: On July 17, 1958 three electrocoagulations of the ventrolateral nucleus of the left thalamus were performed. Tremor and rigidity completely disappeared after the operation. But in the postoperative course tremor and rigidity became gradually worse on the left side. The patient therefore wished to have the same operation on the other side. Right thalamotomy with one coagulation was performed eight months later, on March 5, 1959. This operation resulted in complete relief of tremor and rigidity of the left extremities.

However, on the fourth postoperative day the patient fell out of bed: the fall resulted in a marked confusional state and left-sided hemiparesis, lasting for several months. Two weeks after the fall a generalized epileptic seizure occurred and later three Jacksonian fits developed. Following this, gradual improvement took place over the course of several months, and on examination six months later no abnormality could be found in any extremity. There was no rigidity, no tremor, no Babinski sign. Gait was normal and the patient swung her arms normally in walking. There was no intellectual impairment of any type, and the patient's mood was excellent, and slightly euphoric. After the second operation, however, her speech definitely deteriorated; articulation became slurred, monotonous and faded into an unintelligible mutter. In spite of this symptom the patient is carrying out all of her full-time household duties, which had been beyond her ability before the operation.

Case 2. S.E., a woman aged 39, had suffered from postencephalitic Parkinsonism for seven years and was experiencing painful spasms in the left arm and leg.

On examination the following signs were present: bilateral tremor and muscular rigidity, more marked on the left than on the right; tremor of the lips, slightly slurred speech; moderate mask-type of facies; stiff gait with short steps and without swinging of the arms.

Operation: Right thalamotomy with two electrocoagulations of the ventrolateral nucleus of the right thalamus was performed, and tremor, rigidity and the painful spasms subsided at once on the left side. The second operation, an electrocoagulation of the left thalamus, was performed six months later, in March of 1959. This operation resulted in complete relief of tremor and rigidity on the right side and in a state of apathy, akinesia, salivation and compulsory crying lasting for two weeks. Following this the patient recovered completely. No intellectual impairment could be found, and she is now employed, full-time, as a teacher.

Case 3. P.G., a 59 year old history teacher, had suffered from bilateral tremor and muscular rigidity, disturbance of speech, swallowing and of gait for fifteen years.

On neurological examination, the patient showed the following signs: typical mask-like type of facies, monotone, slurred and unintelligible speech, tremor of the lips, very marked tremor and rigidity of all extremities, more marked on the right than on the left side, stiff gait with short steps and retropulsion. The encephalogram gave evidence of a light symmetrical internal hydrocephalus.

Operation: Left thalamotomy with three coagulations was performed on December 24, 1958, resulting in complete loss of tremor and rigidity on the right side. There was considerable improvement of akinesis and gait; the facial expression became animated and the patient was again able to write. Several months later the second thalamotomy—two electrocoagulations of the right thalamus—was performed: this was followed by complete relief of tremor and rigidity of the left extremities. After this second operation the patient was again able to take care of himself. He has no tremor of the lips, is able to write, and his gait is of normal size, although he still walks without swinging his arms. There is no intellectual impairment; his mood is normal and he is again employed as a teacher of history.

Case 4. D.A., a woman aged 52, experienced a doublesided progressive Parkinsonian symptomatology for five years, first on the left and later on the right side. The malady had considerably impaired her ability to care for herself and her home.

On neurological examination the following signs were detected: Mask-like facies, slow and slurred speech, marked tremor of all extremities, left more than right, moderate muscular rigidity in all limbs, gait with short steps and weakness of the left leg. The pneumoencephalogram showed a ventricular system of normal size.

Operation: A right sided thalamotomy with two electrocoagulations was performed in February, 1959. It resulted in complete relief of tremor and rigidity of the left extremities. Eight months later, on October 1, 1959, thalamotomy with three coagulations of the ventrolateral nucleus of the left thalamus was performed. After the operation the right side was without any evidence of either tremor and rigidity; one month later the patient was still slightly apathetic and depressed, but her orientation in time and place was normal.

Case 5. W.P., a man aged 61, has suffered for 11 years from a bilateral Parkinsonian symptomatology which had failed to respond to conservative treatment, and the patient had reached the point where he was no longer able to work.

On neurological examination, the patient showed the following symptoms: marked mask type of facies, marked salivation and akinesia, slurred, monotonous and unintelligible speech, marked tremor of all extremities, rigidity of a moderate degree, gait with short steps, pro- and retropulsion, and moderate psychoorganic syndrome.

A right thalamotomy with two coagulations was performed on March 24, 1959; it resulted in complete relief of tremor and rigidity of the left extremities. Six months later one electrocoagulation of the ventrolateral nucleus of the left thalamus was performed. This was followed by immediate relief of tremor and rigidity of the right limb. A slight depressive state lasting for a few weeks gradually subsided, and the patient is again employed on a full-time basis.

Case 6. S.S., a 53 year old mechanic, had experienced a leftsided tremor, muscular rigidity and akinesia for nine years and the same symptoms for three years on the right side. For three years he experienced an increasing difficulty in writing, and walking became notably difficult. He was unable to care for himself and he showed forced laughing and crying.

Neurological examination: The patient showed the typical forward flexed posture position with antero- and retropulsion, severe tremor and muscular rigidity of all limbs. His face was like a mask and the hypokinesia was best seen when writing and speaking. There was general poverty of movement, his writing was unintelligible, and articulation was slurred and monotonous. There was a marked bilateral internal hydrocephalus in the encephalogram.

A bilateral thalamotomy was performed in two stages. A left thalamotomy with two electrocoagulations was performed in April of 1959. This operation resulted in complete relief of tremor and muscular rigidity of the right extremities, the antero- and retropulsion subsided and the patient was again able to write. The second operation, a thalamotomy with two electrocoagulations of the ventrolateral nucleus of the right thalamus was performed in October. Relief of tremor and rigidity of the left extremities was complete.

After the bilateral thalamotomy there was no trace of either rigidity or tremor in all extremities. Motor function of the extremities and the gait were normal. The patient's forced laughing and crying disappeared, the facies again showed normal expression and articulation became distinct. No somatic symptoms were noted, and his mental and affective behavior were within normal limits.

DISCUSSION

From a series of 225 operations for Parkinsonism or paralysis agitans, six cases are reported in which bilateral thalamotomy has been practiced and in which the operation has been tolerated without motor, sensory or intellectual loss. In all cases the method of lesion production consisted in stereotaxic coagulation with a current intensity of 150 mA. for a period of twenty seconds. The lesion obtained is large enough for complete relief of hyperkinetic and hypertonic manifestations. The statement of David, quoted by Cooper (1), that he felt the type of stereotaxic operation employing coagulation for small lesions is principally a method of clinical physiologic investigation rather than of therapy, is not confirmed by our own experience. The lesion in the ventrolateral nucleus of the thalamus—the size of 200–250 cmm.—is large enough for enduring and complete results. We confirm the experience of Cooper that a lesion in the region of the ventrolateral nucleus of the thalamus has a more certain, complete, and absolute effect on contralateral resting tremor than does the pallidal lesion. We should like to add that the same is true for rigidity; a well-placed and large enough lesion of the thalamus will change rigidity into hypotonia of the extremities. Therefore, our preference is for the operation which places the lesion at the ventral portion of the thalamus and interrupts all the pallido-thalamic and cerebello-thalamic fibers.

The report of these six cases does not confirm the first experiences of Hassler and Riechert (2), that bilateral thalamotomy may produce severe mental changes. In accordance with Spiegel's (3) statement that a leucotomy effect may be produced by cutting the thalamo-cortical pathways, we have performed the bilateral operation at the level of the coronal suture. Furthermore, it is our impression that on bilateral operations the best results are obtained with few coagulations, *i.e.* one or two. By this method a minimum of the fronto-thalamic pathway is cut. Only in Case 4 of this series is there still some mental impairment with apathy and depression, but the time of postoperative clinical observation is too short for a definite evaluation. The serious transient confusional state in Case 1 was not the

consequence of the surgical intervention but of the cerebral injury from which the patient was suffering.

We agree with Cooper (1) in that only those cases should be submitted to bilateral operation which have tolerated the initial surgical procedure without complication and with a good lasting result. The time interval between the two operations has been at least six months. In five cases there has been a remarkable improvement, with no intellectual impairment.

SUMMARY

The authors' technique of stereotaxic electrocoagulation of the ventrolateral nucleus of the thalamus has been described, and the clinical course of six cases of Parkinsonism discussed. It is shown that in well selected cases an accurately placed bilateral lesion of sufficient size results in no neurological or intellectual deficit.

REFERENCES

1. Cooper, I. S. and Bravo, G. J. Anterior choroidal artery occlusion, chemopallidectomy and chemothalamectomy in Parkinsonism. A consecutive series of 700 operations. In *Pathogenesis and Treatment of Parkinsonism*, Fields, W. S., ed., pp. 326–363. Thomas, Springfield, Ill., 1958.
2. Hassler, R. and Riechert, T. Ueber die Symptomatik und operative Behandlung der extrapyramidalen Bewegungsstörungen. Med. Klin., **53**: 817–824, 1958.
3. Spiegel, E. A. Discussion. In *Pathogenesis and Treatment of Parkinsonism*, Fields, W. S., ed., pp. 354–355. Thomas, Springfield, Ill., 1958.
4. Walker, A. E. Summary of symposium. In *Pathogenesis and Treatment of Parkinsonism*, Fields, W. S., ed., pp. 364–372. Thomas, Springfield, Ill., 1958.
5. Yasargil, M. G., Wyss, O. A. M. and Krayenbühl, H. Beitrag zur Behandlung extrapyramidaler Erkrankungen mittels gezielter Hirnoperationen. Schweiz. Med. Wchnschr., **89**: 143–150, 1959.

BRAIN TUMOR: THE CRUCIBLE OF NEUROSURGERY IN THE PAST THIRTY YEARS

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It is a pleasure to dedicate this paper to Doctor Spiegel, whose accomplishments as a teacher and a research investigator have been so significant. Neurosurgery in the past 30 years has been made possible only by the advances of neurologic sciences, to which our celebrated anniversarius and teacher has contributed so much. Diagnosis and treatment of brain tumors, in particular, have been regarded traditionally as one of the crucibles of neurologic surgery (2, 10). Even today, when this specialty has come of age and diversified its goals, the question, "How many brain tumors do you treat in a year?", represents a certain standard of value to measure the mettle of a neurosurgeon.

In the late nineteen-twenties, neurosurgery was then still in its early stage, although a few leaders had achieved outstanding individual advances. At the time, the recognition of brain tumors was generally entrusted to the neurologist; the neurosurgeon was considered merely a technician who had to be told where and what to cut. Even though a few advanced pioneers were remarkably successful in the diagnosis of intracranial tumors, this field remained largely a *terra incognita* for the common herd; in fact, the possible presence of a brain tumor did not often reach the level of awareness of the general practitioner. As a rule, a brain tumor was not suspected until signs of increased intracranial pressure were severe. Headaches and papilledema were considered *early* manifestations, and it happened all too often that patients with benign tumors reached the neurosurgeon completely blind. Moreover, it was not realized how frequently convulsive seizures were an early indication of brain tumor, or that "strokes" in elderly persons occurred on a neoplastic rather than on a vascular basis.

Thirty years ago, both neurologists and neurosurgeons were preoccupied with the problem of localization, which they approached almost exclusively by clinical means. Thus, the accuracy of diagnosis remained low and even in the hands of the most experienced did not exceed 60–70 per cent. Cushing early recognized that knowledge of anatomic tumor type was highly important. He was able to describe certain varieties of tumor with clearly characterized clinical features as specific clinicopathologic entities (pituitary adenomas, acoustic neuromas). Later on this approach was extended to other hitherto inadequately classified groups, such as the gliomas and meningiomas.

In the late nineteen-twenties, neuroroentgenology was still in its infancy, yet it rapidly gained recognition and stature. The methods of pneumography (3) were eagerly adopted by most neurosurgeons but intracranial angiography (5) was not yet known.

It is not surprising that in those days brain tumors were missed entirely or diagnosed too late to be benefited by surgical treatment. All too many patients with rapidly progressive lesions must have died by the wayside before they reached a neurosurgeon. The statistics of the leading neurosurgeons of that era, therefore, give no true picture of the actual incidence of the various tumor types in the general population. In Cushing's series, for example, pituitary adenomas and acoustic neuromas attained a surprisingly high percentage figure; on the other hand, his figures for glioblastomas and metastatic lesions were far below those found

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in statistics of large general hospitals. As neurologists struggled with the uncertainties of diagnosis and often procrastinated in order that additional clinical signs might eventually clinch a particular diagnosis, the neurosurgeons fought desperately with the problems of increased intracranial pressure. The more cautious surgeons were inclined to limit themselves to a conservative or even palliative approach hoping to reduce their mortalities.

A few daring surgical "naturals" with uncanny technical skill, however, tackled any brain tumor regardless of the odds and outcome. The medical profession in general took a doubtful, but essentially pessimistic, view of the surgical results in brain tumors; nevertheless, the outstanding achievements of a few masters were acknowledged with a mixture of incredulity and awe. For their contemporaries, these neurosurgeons became the heroes of their epoch just as the cardiac surgeons are the "glamour boys" of our present medical generation. We certainly must admire the courage and skill of these neurosurgical pioneers, considering their handicaps and limitations.

Tremendous changes have taken place in the past 30 years. Not only has the compounded knowledge of all neurologic sciences expanded, but medical information concerning this area has grown among physicians and laymen alike. The advances in technical and laboratory methods have been phenomenal. In the nineteen-twenties, fewer than a score of neurosurgeons gathered the centrifuged sediment of carefully selected neurosurgical patients from the entire country; patients came hundreds of miles to see a neurosurgeon and travelled across continents to be operated upon by a master. Thus, a single neurosurgeon could achieve a prodigious concentration of clinical material and experience. In contrast, there are now over one thousand highly trained neurosurgeons practicing in the U. S. A. Many of these men have settled even in smaller communities, with populations of less than 100,000. This has obviously produced an atomization of the clinical material and, therefore few except the staff of a few big centers see as many brain tumors as in the earlier period. Unlike the situation in the U. S. A., neurosurgeons in countries like Sweden, Great Britain and U.S.S.R. are still few in number, and thus able to accumulate large numbers of cases.

In our present day, the general practitioner, the osteopath, the chiropractor and even the layman are quite aware of the existence of brain tumors. Folklore, movies and popular literature have unfortunately created here a false cliché of the dreaded brain tumor. A patient suffering from severe headaches may say, "My headaches *feel* like a pressure" and then, in his anxiety, may irrationally conclude that they must indeed be produced by pressure—he is *sure* he has a brain tumor. If the first consulted physician fails to dispel the patient's fear or confirms the remote possibility of an intracranial neoplasm, the patient will certainly see a neurosurgeon. This species of the "iatrogenic pseudotumor" is the scourge of neurosurgical office practice; in fact, 95 per cent of these people have no organic intracranial disease at all. While the spectre of brain tumor may haunt the anxiety-neurotic, and minimal organic symptoms may be beclouded by functional overlay, at least patients now seek medical care earlier than in the past. The clinical neurologic examination which amounts to a crude pathophysiologic evaluation at a given time is not always a sufficiently sensitive index of what is going on inside the skull. Fortunately, we possess more refined and precise techniques of investigation: the EEG for physiologic study and the roentgenographic examination (including contrast methods) for anatomic study. Early and judicious use of these ancillary techniques permits one to screen out the "brain tumor suspects." Perhaps the neurologist of the old school may bemoan the declining respect for clinical examination among the younger neurosur-

gical generation, but at present the diagnosis of brain tumor is surely made more accurately and earlier than in the past. For example, a correct diagnosis may be made after a few seizures, even though no neurologic deficit exists. Only a third of the brain tumors observed in the writer's practice were found to be associated with papilledema. I have noticed that the average size of the surgically removed meningiomas has been diminishing in recent years: whereas in the past, specimens weighing between 100–200 gms. were quite common, they now weigh usually less than 100 gms. Patients blinded by brain tumors, fortunately, have become rare (except in chiasmal lesions).

It is necessary to discuss the relative merits of the ancillary techniques in some detail. The EEG (1) has proven its value mainly in supratentorial lesions, confirming localization, or at least lateralization. The EEG is a harmless screening method for the ambulatory patient or for the semiconscious, uncooperative individual. Under such conditions, demonstration of a pineal shift on plain roentgenograms is of additional help. Lateral displacement of the pineal shadow may decide on which side arteriography is to be performed.

The almost universal use of ventriculography in the thirties has been substituted by its more selective indication in tumors of the posterior fossa, brainstem and of the ventricular system.

Pneumoencephalography without removal of cerebrospinal fluid has now become popular, even in cases with marked increase of intracranial pressure; most of the older neurosurgeons, however, have been reluctant to employ this method too liberally. In supratentorial lesions, angiography has practically replaced the pneumographic methods because of its greater safety and the possibility of demonstrating not only location but also anatomic type of the lesion.

The importance of routine roentgenograms of the chest cannot be overemphasized in brain tumor suspects. First, intracranial metastasis from an asymptomatic malignancy of the chest is surprisingly common; second, preoperative inflammatory bronchopulmonary complications should be known before one risks craniotomy under general anesthesia.

The diagnostic use of radioisotopes has been well-established as a safe screening procedure (8), but it lacks the accuracy and reliability of the roentgenographic methods, since certain tumor types show little uptake of the tracer substance.

To summarize, the selective or combined use of the present diagnostic procedures enables the neurosurgeon to make an accurate localization of brain tumors in more than 95 per cent of the cases and surmise the anatomic type in more than half.

All the spectacular advances in the past 30 years are mainly due to systematic application of scientific physiologic thinking to clinical problems. This approach provided an understanding of the life history of brain tumors. Investigations concerning the production and resorption of cerebrospinal fluid, intracranial pressure, brain swelling, cerebral circulation, water and electrolyte balance and the hormonal control have vastly increased our knowledge of preoperative and postoperative management. A good example for the progress made by the physiologic approach is the development of neurosurgical anesthesia. A few decades ago, the anesthetist was an empirically-trained technician who served the whims and wishes of the surgeon and occasionally added to the burdens of the operator instead of lightening them. The modern anesthesiologist is a practicing physiologist in his own right who coordinates his activities with, rather than subordinating them to, the work of the surgeon. He watchfully maintains adequate airway and oxygenation, controls the intracranial pressure, *e.g.*, by use of urea (4), replaces blood loss and protects the sensitive

neuronal tissue against the deleterious effects of impaired blood circulation by hypothermia (7). As the anesthesiologist takes care of the patient as a whole, he leaves the surgeon free to concentrate on the local problem.

Neurosurgical technique *per se* has changed relatively little in the past 30 years, yet there have been some refinements, chiefly concerning the means of hemostasis (diathermy, gelfoam, induced hypotension). As the trial and error period of neurosurgery has come to a close, the technical steps have become largely standardized. Finally, another very significant factor must not be overlooked—the personality and attitude of the neurosurgeon have changed too. Gone are the days of barnstorming enthusiasm and surgical bravado. Brain tumor surgery is no longer simply a game of keeping down one's mortality score. The age of prima donnas and the sense of uniqueness have passed. There are now very many and equally capable neurosurgeons, and they tend to work in teams rather than remain rugged individualists. Being more sophisticated than their predecessors, they are willing to take a considerable number of calculated risks without being frightened by mortality statistics, but they shun unnecessary radicalism in inoperable lesions. They are apt to be conservative in the sacrifice of brain tissue for mere mechanical advantage, because their physiologic orientation has filled them with respect for the miraculous function of the nervous system. Although the mortality figures were amazingly low in Cushing's series, further reduction has been accomplished for certain tumor groups (meningiomas, acoustic neuromas). The risk of surgical intervention in the hypothalamohypophyseal region has been greatly diminished by the use of corticosteroids (9). Our methods of palliation are more discriminative, and therefore, more effective than those practiced 30 years ago, *e.g.*, shunt procedures have replaced simple decompressions in certain cases of obstructive hydrocephalus. Therapeutic irradiation of brain tumors has become a welcome adjunct of surgical treatment. The traditional roentgenray therapy has been perfected and supplemented by other techniques such as cobalt-, neutron-, and proton irradiations.

Looking to the future, we realize that the problem of brain tumors cannot be solved by purely surgical means. Although surgical technique in intracranial tumors has been perfected to a very high degree, as in other types of cancer, a purely mechanistic approach cannot be the ultimate answer. When we will have reached a deeper understanding of the underlying causes, and especially of the biologic and chemical behavior of neoplastic tissue; we may be able to detect conditions leading to the development of tumors earlier, and to prevent or selectively destroy neoplastic cells by the action of drugs or special forms of irradiation, rather than to resort to crudely ablative techniques.

Recently attempts have been made to annihilate neoplastic cells by introducing antimetabolites, such as nitrogen mustards, into the isolated cerebral circulation, utilizing an extracorporeal perfusion technique (6). Such chemotherapeutic methods might prove eventually successful, provided an agent with highly selective toxicity can be found.

REFERENCES

1. Bucy, P. C. The clinical use of electroencephalography. J. Neurosurg., **14**: 442–447, 1957.
2. Cushing, H. *Intracranial Tumors. Notes upon a Series of 2000 Verified Cases with Surgical Mortality Percentages Pertaining Thereto.* Thomas, Springfield, Ill., 1932.
3. Dandy, W. E. Ventriculography following injection of air into the cerebral ventricles. Ann. Surg., **68**: 5–11, 1918.
4. Javid, M. Urea; new use of an old agent, reduction of intracranial and intraocular pressure. Surg. Clin. N. America, **38**: 907, 1958.
5. Moniz, E. *Diagnostic des tumeurs cérébrales et épreuve de l'encéphalographic artérielle.* Masson, Paris, 1931.
6. Ryan, R. L., Axelrod, A. J. and Whitney, D. G. The development of technics for the isola-

tion-perfusion of brain. 27th Ann. Meeting, Harvey Cushing Society, New Orleans, Apr. 30–May 2, 1959.

7. SEDZIMIR, C. B. AND DUNDEE, J. W. Hypothermia in the treatment of cerebral tumors. J. Neurosurg., **15**: 199–206, 1958.
8. SWEET, W. H. AND BROWNELL, G. C. Localization of intracranial lesions by scanning with positron emitting arsenic. J. A. M. A., **157**: 1183–1188, 1955.
9. TYTUS, J. S., SELTZER, H. S. AND KAHN, E. A. Cortisone as an aid in the surgical treatmen of craniopharyngiomas. J. Neurosurg., **12**: 555–564, 1955.
10. WALKER, A. E. *A History of Neurological Surgery*. Williams & Wilkins, Baltimore, 1951.

A VERSATILE MULTIPLE-CHOICE APPARATUS FOR THE STUDY OF ANIMAL BEHAVIOR[1]

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Investigations establishing and approximating the variables and parameters of conflict essential to the development of an "experimental neurosis" have given especial recognition to the role of aversive stimuli, while clinical observation has also testified the import of nonaversive stimuli (12). It is evident that experimental validation of idiomorphic clinical phenomena such as severe anxieties, symptom formations, and defensive reactions correlated with decisions between or among desirable objects (*e.g.*, mutually exclusive careers or spouses) would denote *conflict* rather than fear alone as the theoretic key to the etiology of neurotic behavior.

Burodin and others have examined restricted facets of this problem. Different specific arrangements of attractive goal objects have yielded behavioral indicants of conflict in fish (7), birds (17), ape (5), and children (2–4) but peculiarly not in rats (10, 19) or college students (1). These data, although specifying the influence of certain factors (*e.g.*, certainly, symbolic *vs.* actual choices, innate responses, age, etc.) on adaptational patterns involving nonaversive stimuli, were either incidental to their immediate studies or entirely tangential to the dynamics of neuroses.

METHOD

The present approach derives from research oriented to the functional properties of "normal" and "neurotic" behavior (13), and as such demands instrumentation permitting a representative sampling of the event in question. We have, therefore, designed and constructed a flexible apparatus to explore the responses of cats and monkeys to conflict involving *nonaversive* stimuli. It is significant that this apparatus provides an observational situation distinct from that outgrowth of behaviorism epitomized in the history of the Skinner-box (18) without departing from an operational frame of reference.[3] The apparatus employs a wide range of stimuli in different sensory modalities for the study of representational generalizations (sign or symbol formations) and their influence on goal-oriented aspects of behavior in multiple-choice situations.[4] The efficiency of this approach is enhanced by additional observations of the animal's behavior in an experimental cage specifically designed and constructed for the study of (a) spontaneous and learned patterns of behavior in normal cats and monkeys, (b) alterations of these patterns during and after the induction of experimental neuroses, or (c) the administration of drugs with or without brain lesions (14) and in a discrimination apparatus modelled on those of Klüver and Harlow (8, 11).

[1] This investigation was supported in part by a research grant M-2312 from the National Institute of Health, Public Health Service, and a grant from the Mental Health Fund of the Illinois Department of Public Welfare.

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[3] Bertrand Russell expresses the methodological point as follows "The general principle of relativity showed that, in expressing the laws of macroscopic physics, we can transform our coordinates in any way we choose, so long as topological relations in space-time are preserved as topological relations among coordinates. It follows that the laws of macroscopic physics are topological laws, and that the introduction of number through coordinates is only a practical convenience, the laws being such as can, in theory, be expressed without the use of number. The old view that measurement is of the essence of science would therefore seem to be erroneous" (16).

[4] Other "multiple-choice" apparatus have been described for the selected problems of perseverance in an insoluble situation (6), delayed reaction (9) and complex relational cues (20).

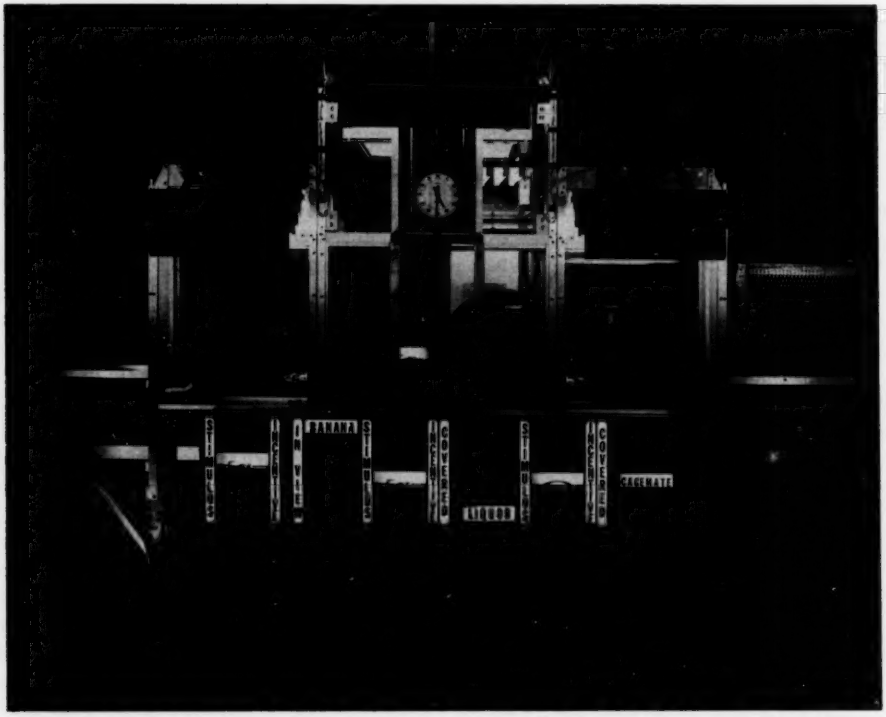

FIG. 1. Male choosing among banana, liquor, and female cagemate in the multiple-choice apparatus.

APPARATUS[5]

BASIC FEATURES

The main units of the apparatus are illustrated in Figure 1. It consists of a chamber (31 x 30 x 22 inches) surrounded on three sides by portable compartments (15 x 22 x 22 inches). The structures are composed of ¼ in. safety plate glass, extruded aluminum frameworks, stainless steel floors and wood foundations. Entrances and exits are provided by a spring-balanced glass door at the front of the chamber; Plexiglas doors lead from the chamber to each compartment and from each compartment to a transport-cage. The inner doors are raised and lowered by motors, have movement-limiting micro-switches and self-locking mechanical latches. Push-pull levers in the chamber and compartments can activate the doors as well as the stimuli and reward systems described below. These levers operate with a minimum of 1 oz. of pressure and ⅛ inch of movement. The apparatus is ventilated through the ceiling of the chamber by a blower which moves approximately 14 cubic ft. of air per minute. This arrangement provides for replacement of the entire air content of the chamber every 30 seconds and also for control of olfactory cues associated with specific compartments, each of which can be clamped to the chamber, removed or interchanged. Each division of the apparatus can be seen from all others except when one or more sections are suitably covered.

[5] Dr. Curtis Pechtel, Mr. Thomas McAvoy and Mr. Russell I. Smith conrtibuted to the design and construction of the apparatus; Mr. George Dold designed and completed the electrical system.

COAL OBJECTS

A gear-driven rotary magazine provides automatic delivery and removal of ten dishes to and from a holder at the rear of each compartment. Each dish can carry the maximum of a 2¼″ cube of solid food or 30 cc. of liquid; both rewards may be hidden from view by opaque lids. Experimental control and flexibility in the use of liquids is accomplished by an electrically timed solenoid valve which accurately deposits ½ cc. to 45 cc. into a dish made available in

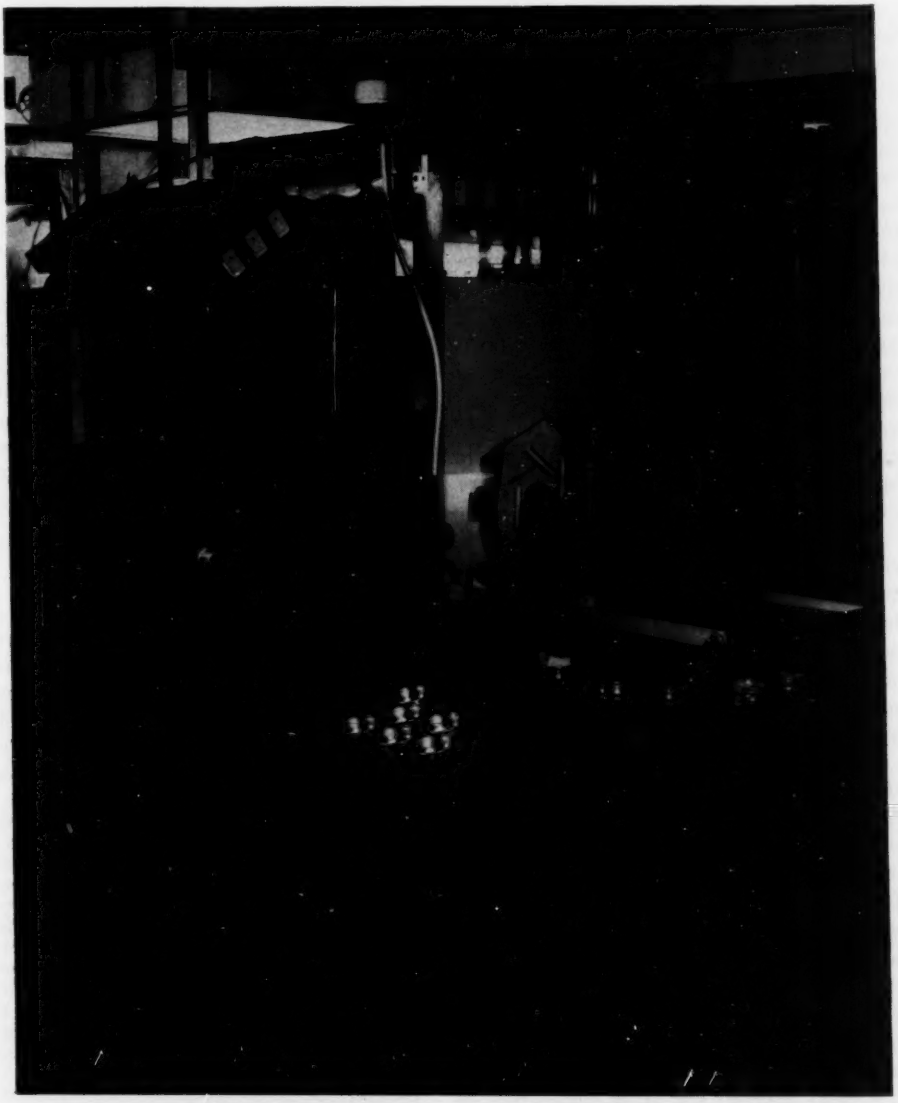

FIG. 2. Rear view of compartment showing visual stimulus mechanism, liquid and solid feeding systems, and construction of floor level controls.

the holder. These feeding devices are shown in Figure 2. Other goal objects such as toys, animals of the opposite sex, offspring, etc., can be previously placed in the compartments.

STIMULI

Visual: Stimulus mechanisms which may be located directly in front of the chamber levers or behind and over the goal objects are used in the control and variation of multiple visual dimensions. In Figure 2 the cover has been removed from one to show the essential parts. The hexagonal frame contains a 4 watt Daylight fluorescent lamp at its center and a stimulus holder (7 x 1¾ x 2 inches) on each side. Thus, a three-choice situation offers 816 different combinations of lighted presentations and 2024 with the inclusion of non-illuminated presentations. Each compartment has a signal lamp close to its lever and can receive projected pictures through a translucent screen on its rear door. The light intensity can be varied independently for any region of the apparatus.

Auditory: The apparatus is equipped with bell and buzzer signals which can be synchronized with the clock employed in the measurement of response latencies. The buzzer signals can be varied in both intensity and spatial location. Speakers can be localized within compartments to present tape-recorded material.

Somesthetic: One compartment can be adjusted in ½ inch steps up to 7 inches above or below the floor level of the chamber. The size of door openings leading to the compartments can be varied. The influence of spatial orientations on behavior can be assessed through seven permutations of four basic unit combinations. Each unit has a stainless steel grid which can be removed to facilitate cleaning. Harmless shocks of pulse nature (open circuit 6000 v., 1–100 ma. constant current range, 500 microseconds every second) can be administered to the animal through the grid. The shock circuit permits the use of limiting resistors to provide different degrees of shock dependent upon the animal and grid conditions.

Central Nervous Stimulation: This apparatus is being equipped for distant stimulation of cerebral structures by radio waves which activate stereotactically implanted electrodes.

ACTIVITY AND RESPONSE RECORDING

"Spontaneous" activity, orienting, vacillation, and lever responses are recorded on counters and kymograph. Each compartment entrance with its adjacent lever and the central region in the choice chamber, and each compartment reward area is demarcated by photoelectric cells. The central zone (or signal area) of the chamber is covered from above by an adjustable photoelectric cell operated through light reflected off the grid floor. The other units consist of six watt incandescent light sources with Kodak No. 88A filters which provide almost invisible pencil beams six inches above floor level to Clarirex Type CL403 photoelectric cells fitted with Wratten No. 29 filters.[6]

CONTROLS[7]

Wires from all electrically operated systems are led through a connector-panel and five detachable multiwire cables to a movable master control panel (see Figure 3) from which the apparatus is operated. The electrical system is shown schematically in

[6] Illumination and photography: The interior of the apparatus is provided with Daylight fluorescent lighting as follows: chamber-overhead, six 20-watt lamps; front, three 20-watt lamps; compartments-overhead, five 15-watt lamps; front, three 15-watt lamps; providing adequate light for motion-picture photography with either an f3.5 lens and Plus-X or f6.3 and Tri-X film. The signal lights next to the compartment levels and a display panel bearing the stimulus incentives can be synchronized with various non-visual stimuli, thus rendering the film an objective record of the entire experimental procedure.

[7] Wiring diagrams, descriptions of specific components of the apparatus and experimental sequences governed by the control panel are available on request.

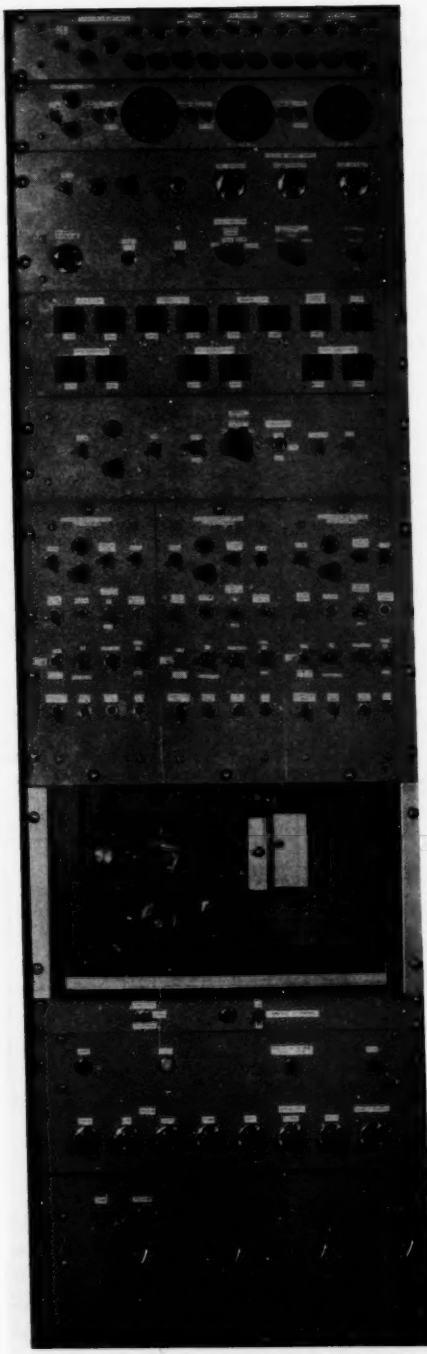

FIG. 3. Main control panel of multiple-choice apparatus.

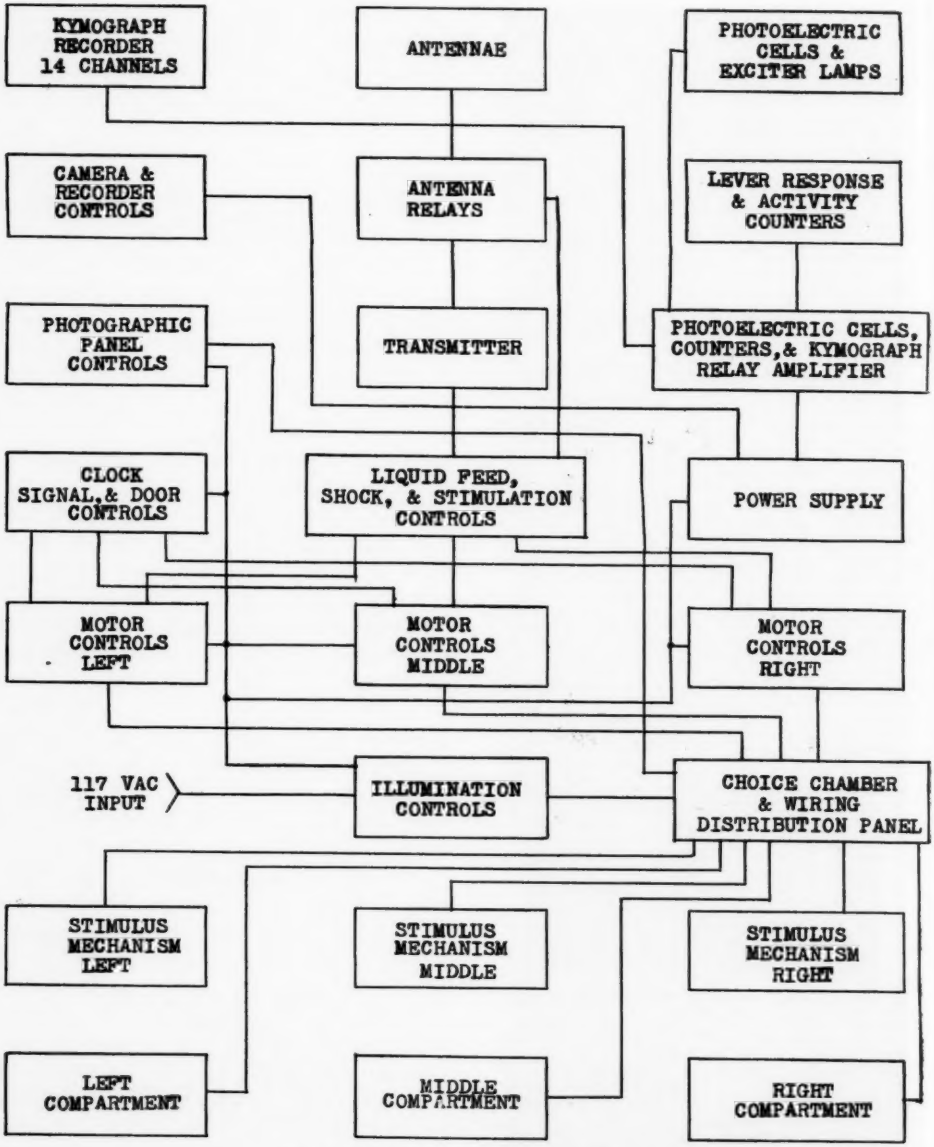

FIG. 4. Block diagram of electrical system.

Figure 4. Several important characteristics of the master controls are as follows: a) noiseless spring-leaf switches for intra-trial and session operations; b) independent but not mutually exclusive control of the doors, stimuli and reward systems by the animal and the experimenter; c) independent controls of all basic features for each of the four units; d) reset counters, kymograph and chronoscope controls for highly reliable

recording of signals, frequency and time parameters of varied performances; and e) controls for the sensitivity of all photoelectric cells.

REFERENCES

1. ATTHOWE, J. M., JR. Decision making and conflict resolution. Paper presented at the 66th annual convention of the Am. Psychol. A., Washington, D. C., July, 1958.
2. BARKER, R. G. An experimental study of the resolution of conflict by children. In *Studies in Personality*, McNemar, Q. and Merrill, M. A., eds. McGraw-Hill, New York, 1954.
3. BEALE, E. A. A developmental analysis of children's delay behavior in a temptation-type of conflict situation. Paper presented at the 38th annual meeting of the Western Psychol. A., Monterey, Calif., April, 1958.
4. GODBEER, E. *Factors inducing conflict in the choice behavior of children*. Dissertation. Yale Univ., New Haven, 1940. Cited in no. 15 below.
5. GUTHRIE, E. R. *The Psychology of Human Conflict*. Harper, New York, 1938.
6. HAMILTON, G. V. A study of perseverance reactions in primates and rodents. Behavior Monogr., **3**: 1916.
7. HARALSON, J. V. AND TYSON, R. Approach-approach conflict in fish. Paper presented at the 39th annual meeting of the Western Psychol. A., San Diego, Calif., April, 1959.
8. HARLOW, H. F. The formation of learning sets. Psychol. Rev. **56**: 51–65, 1949.
9. HUNTER, W. S. The delayed reaction in animals and children. Behavior Monogr., **2**: 1912.
10. KLEBANOFF, S. G. *An experimental analysis of approach-approach and avoidance-avoidance conflict*. Dissertation. Yale Univ., New Haven, 1939. Cited in no. 15 below.
11. KLÜVER, H. *Behavior Mechanisms in Monkeys*. Univ. of Chicago Press, Chicago, 1933.
12. MASSERMAN, J. H. *Behavior and Neurosis*. Univ. of Chicago Press, Chicago, 1943.
13. MASSERMAN, J. H. Experimental psychopharmacology and behavioral relativity. In *Problems of Addiction and Habituation*, Hoch, P. and Zubin, J., eds. Grune & Stratton, New York, 1958.
14. MASSERMAN, J. H. AND PECHTEL, C. Neuroses in monkeys: A preliminary report of experimental observations. Ann. New York Acad. Sc., **56**: 253–265, 1953.
15. MILLER, N. E. Experimental studies of conflict. In *Personality and Behavior Disorders*, Hunt, J. M., ed., Vol. 1, pp. 431–463. Ronald Press, New York, 1944.
16. RUSSELL, B. On the importance of logical form. In *Encyclopedia and Unified Science*., Neurath, O., ed. Univ. of Chicago Press, Chicago, 1946.
17. SAUER, E. G. F. Cited in Lorenz, K. Z. The deprivation experiment: Its limitations and its value as a means to separate learned and unlearned elements of behavior. Paper presented at V. A. Hospital Training Program, Downey, Ill., October, 1958.
18. SKINNER, B. F. A case history in scientific method. Am. Psychologist, **11**: 221–233, 1956.
19. WILLIAMS, S. B. A note on approach-approach conflict in rats. J. Comp. Psychol., **35**: 269–274, 1943.
20. YERKES, R. M. AND COBURN, C. A. A study of the behavior of the pig Sus Scrofa by the multiple-choice method. J. Animal Behavior, **5**: 185–225, 1915.

THE COURSE OF VASODILATOR FIBERS IN THE SPINAL CORD

LEWIS J. POLLOCK, M.D.[1] AND BENJAMIN H. KESERT, M.D.[1]

It is fitting that in a Festschrift for Professor Spiegel that a study on the spinal pathway of the vasodilators should be included, for as early as 1932 (4), and later with Hunsicker (5), he studied the condition of cortical impulses to the autonomic nerveous system.

The purpose of this presentation is to report briefly on over 1200 patients suffering from paraplegia and quadriplegia, who have been observed at the Veterans Administration Hospital, Hines, Illinois. In most of these cases, cold pressor studies were made, as well as studies on the effect of bladder and rectal distension (Pollock *et al.* (3)).

In this note we shall restrict ourselves to but a few cases in whom catastrophic drops in blood pressure (as much as 86 mm of Hg.) occurred in association with the cold pressor test; in fact, some of the extremities had become pulseless. For the sake of simplicity, we shall not describe the changes of stimulation of one on another extremity, nor theorize about hypothalamic and other effects.

The cases of which we speak were all limited to lesions of the cervical spinal cord and only those in whom the result of the lesion simulates a thrombosis of the anterior spinal artery; namely, that the posterior portion of the spinal cord was intact.

Of many cases of injury to the cervical spinal cord, in only twelve were we able to demonstrate these falls in blood pressure.

In 1937, Grimson, Wilson and Phemister (1) demonstrated the effect of sympathectomy on the usually observed rise in blood pressure when the intracranial pressure is raised. After sympathectomy, although the expected rise in blood pressure did not occur, they reported that vasodepressor responses were still obtainable.

There is much to suggest that the vasoconstrictors descend along with the corticospinal tract. Thus Spiegel (4) noted a fall in blood pressure after severing the pyramidal tract.

Kell and Hoff (2) concluded that the descending pressor pathway in the cord at the lower cervical level runs in a relatively narrow zone at the junction of the dorsolateral and ventrolateral funiculi. This, they maintained, coincides with Foerster's localization of the descending vasomotor pathway in man.

In four of our cases, we were able to study the relation of recovery of motor function to changes in blood pressure. We found that when motion recovered, the severe falls in blood pressure ensued upon the cold pressor test, suggesting that the vasoconstrictors travel along with the corticospinal tract.

In summary, it would appear that a catastrophic drop in blood pressure results from the application of cold to an extremity in some lesions of the cervical spinal cord. These lesions occupy the anterior portion of the spinal cord. From the observation that when motor function returns, stimulation results in a fall in blood pressure, it is suggested that the descending vasoconstrictors and vasodilators descend in different columns of the spinal cord. The vasodilator fibers occupy the posterior portion of the spinal cord.

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REFERENCES

1. GRIMSON, K. S., WILSON, H. AND PHEMISTER, D. B. The early and remote effects of total and partial paravertebral sympathectomy on blood pressure. Ann. Surg., **106**: 801–823, 1937.

2. Kell, J. F., Jr. and Hoff, E. C. Descending spinal pathways mediating pressor responses of cerebral origin. J. Neurophysiol., **15**: 299–311, 1952.
3. Pollock, L. J. and others. The management of residuals of injuries to spinal cord and cauda equina. J. A. M. A., **146**: 1551–1562, 1951.
4. Spiegel, E. A. The centers of the vegetative system. Bull. Johns Hopkins Hosp., **50**: 237–252, 1932.
5. Spiegel, E. A. and Hunsicker, W. C. The conduction of cortical impulses to the autonomic nervous system. J. Nerv. & Ment. Dis., **83**: 252–274, 1936.

PROGRESSION AND PROGNOSIS IN PARKINSON'S DISEASE

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INTRODUCTION

In a number of clinical papers on Parkinson's disease that have appeared in the last ten years, a most pessimistic note dominates the text particularly in regard to progression and prognosis. For example, in the rather brief summary of Miller (4) it is stated that Parkinson's disease is characterized by steady, inevitable progression of symptoms so that after seven to eight years from onset the patients are usually completely dependent on others for their every-day activities. Release from this hopeless state by death from intercurrent infection and malnutrition soon follows.

In many texts (1, 6) progression is described as always characteristic of the disease and it is stated that little specific and objective help can be given to relieve the symptoms or improve the general clinical state of the patient. It is certainly true that real remissions of the disease are unknown and any type of so-called cure is never encountered by those working with this disorder. The gloomy picture of the inevitable invalidism after seven or eight years with demise soon after is not a picture of the true state of the disease. This communication will bring evidence that many patients develop the disease slowly and have minimal signs and symptoms that do not progress in any measurable way from year to year. Some cases are associated with almost no general disability. It will be shown, also, that some patients, after as many as twenty-five years since onset of the disease, are still independent of aid in eating, dressing, walking, doing ordinary chores around the house, and even their work. They have fully learned to adapt themselves to the annoying or embarrassing features of Parkinson's disease that are not necessarily associated with disability. It must be admitted, on the other hand, that some patients develop their disease in a relatively rapid manner so that in two or three years after onset they are so handicapped that they can be regarded as nearly totally invalided. However, this is the exception. In short, the evidence that we have uncovered in the continual study of these patients, under a special Parkinson Clinic investigational program involving 800 individuals, points out that two-thirds of the living patients (110 of the 800 have died, leaving 690 remaining) are still ambulatory and independent. They dress and feed themselves and can move about freely without help. Only one-fifth of this number are classified as totally invalided and fully dependent. Our material indicates that no one patient is the same as another and that there are many types of disability and invalidism. There are also a large variety of different levels of progression in this disease; these will be discussed below.

The Parkinson cases that compose our large series come from those referred to the special clinic in the Neurological Out Patient department. This has been in operation since 1948. In addition, the private patients of the writer and his associate, who have come to the office or have been admitted to the hospital for a period of clinical investigation, are included. It is immediately evident that this group of patients is somewhat artificially selected in that the severe bedridden patient who is totally invalided is rarely seen under this setting. We have seen very severe cases of tremor, in some instances bilateral, so extreme that the recording instrument is almost unable

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to measure the tremendous amount of shaking. We have seen rigidity that reaches our maximum value of four plus (++++) on both sides, which has left the patient nearly totally unable to perform any kind of useful act with his hand. But even these patients are ambulatory, in general, or have come to the clinic or office in wheel chairs. The institutionalized patient, totally incapacitated and showing evidence of other medical disease, and frequently evidence of dementia, is not seen in our group; nor would we encourage the hospital admission of such a patient. On the other hand, we have seen patients who were rapidly progressing and, at the time of their examination, were still ambulatory and only partially incapacitated. These patients, after a number of years, have had to enter nursing homes or institutions for their complete care. We have data concerning them which balances those milder cases with better prognosis and slower progression.

At this point it might be well to define what is meant by progression and prognosis. An attempt will be made to give these two categories some objectivity by numerical classification. Progression, as we define it, is adverse change or increase in symptoms in the disease over a period of time. It is obvious that in dealing with reversible medical conditions, such as pulmonary inflammation, progression is both positive and negative and the patient eventually makes a full recovery, going through both phases. This is to some degree also true in Parkinson's disease. Patients may advance with their symptoms and disability to a certain degree and then respond to either medical, physiotherapeutic or surgical measures, returning at least in part to a normal level of health. Progression of the disease must be separated from the natural aging process of the individual over the years, and also should be separated from the development of other diseases which impair the patient's health and performance.

Prognosis may be defined as the estimate of the amount of progression that is going to occur in the individual in the immediate and relatively distant future and, therefore, could be regarded as a reciprocal of progression.

For convenience it might be well to divide progression into five grades.

Grade 5 is the most rapid. Here the disease begins rather abruptly and spreads within a few months to involve both sides of the body. It is associated within the first year after onset with marked degrees of incapacity and motor deficiency. Severe amounts of tremor and rigidity are encountered, and it is nearly always associated with considerable amounts of akinesia. Such patients are severely handicapped within a year or two of onset and become completely invalided, usually within three to four years of the onset of symptoms.

Grade 4 is defined as a considerable degree of progression. Here the disease develops more slowly over several years before the condition can be noted on both sides. At the end of three to five years the patients are still ambulatory but severely involved with the disease. Symptoms of tremor and rigidity are usually present on both sides. Such patients usually do not become invalided until eight or ten years have elapsed.

Grade 3 is a moderate involvement. In such cases the disease frequently remains on one side only, and a period of three to five years may elapse before any noticeable incapacity is encountered. Such patients are able to work and usually are completely independent after ten years with the disease. They have definite signs of the disorder and frequently minimal signs are present on the opposite side. It may be as long as fifteen years before the symptoms are sufficiently advanced as to invalid them totally.

Grade 2 signifies a mild progression. It is

nearly impossible to note any difference in such patients from year to year. After a period of five to six years it is quite easy to show evidence of progression, but such patients usually remain largely independent until their death from other causes. There is no question concerning the diagnosis, and over a number of years there is no question about the presence of some progression. In such cases the disease may remain entirely on one side, with no evidence of bilateral symptoms.

Grade 1 is a slight amount of progression: this group involves those patients who present diagnostic problems as to whether they do or do not have Parkinson's disease. Their symptoms are so slight and they are so nearly completely without disability that the ordinary practitioner would hesitate to make a diagnosis. An experienced neurologist usually has no difficulty in demonstrating a slight loss of associated movements on one side, a bit of awkwardness in fine finger movements, a little loss of facial expression, and sometimes a minimal amount of cog-wheel rigidity. If these patients are under stress sometimes a bit of resting tremor can be elicited. Such patients who show this amount of disorder do not change from year to year and at the end of considerable periods of time, particularly if small amounts of therapy are given, may present the identical picture five years after the initial examination. They never become dependent due to Parkinsonism and it is usually not a threat to their economic existence or their life at large.

Since this disease is characterized by an extreme variability of symptoms, from hour to hour and day to day, it is essential that some effort be made in the direction of careful objective measurements of motor performance, as well as subjective estimation of mental ability at every office or clinic visit. Even with the most careful appraisal it is not always easy to be sure of the absence or presence of progression. Some of these objective and subjective measurements will be described later.

If a patient with this disease is subjected to a severe stress, such as a death of a loved family member, severe financial loss, or a disturbing automobile accident; there may be a temporary progression of symptoms. In some patients this disappears after a period of time. It is true that in other cases this situational aggravation of the disorder remains permanently. Such factors as these have to be considered in determining progression but obviously cannot be anticipated in discussing prognosis. One must guard against the patient's relatives who watch with intense interest and concern the different symptoms that the patient may have daily; they soon learn to detect more subtle differences through experience. Relatives may report at the end of a year that the patient is "deteriorating" when all that has happened is that the spouse has learned to identify a large number of minor symptoms which he or she was unaware of at the beginning.

Patients overly concerned with their own health and necessarily introspective, may be guilty of the same artificial learning of the subtle differences in their motor behavior, which they interpret as disastrous and rapid progression.

OBJECTIVE MEASUREMENTS OF THE AMOUNT OF PROGRESSION AND DISABILITY

Since 1948 we have been evaluating a large variety of objective tests of motor performance in patients with Parkinson's disease. It is obvious that if one is to measure the amount of progression of the disorder between two periods of observation, for example, twelve months apart, there has to be a number of different functions that can be measured, making allowances for the different levels of motivation and the ordinary variations that patients show from time to time. Our conviction at this time is that, given at least six different

tests which are accurate and simple enough to be done without fatiguing the patient, they will yield a reasonably accurate indication of the presence or absence of progression.

In addition to these so-called objective tests, it is important to obtain from the patient an account of his motor performance in relation to these activities prior to the disease, and to quantify this in some way so that it can be compared with earlier and later similar estimations. Although this is a subjective estimation, it is often as important as the objective one in arriving at a correct measurement of the presence of progression. There is no need to discuss those tests which we have found to be too complicated or too inaccurate and which have been abandoned over the past twelve years. The tests we rely on at the present time are as follows.

1). Time with a stop watch the number of seconds it takes the patient to walk over a 10-meter course as rapidly as possible. During this time it is noted whether the arm swings, whether the patient scuffles, whether the posture is bent, and the number of steps taken.

2). The patient draws a 4-inch circle with a pencil as rapidly as he can, until he has completed 10 circles. In order to assist him, a printed circle is on the sheet and he is told to follow this line around. A stop watch is used to measure the time it takes to draw these ten circles. In addition to showing slowness in this motor act, this test will also show the ability to maintain the diameter of the circle. Unless they are repeatedly warned, some patients tend progressively to decrease the diameter. Tremor of an intention type shows up easily on this test, which is completed with both the right and left hands.

3). Since 1951 we have used a bulb ergograph in the examination of every patient on each visit. This produces a fatigue curve, the bulb being held first in one hand, and then the other. This apparatus is designed so that a normal person, squeezing the bulb once per second, can maintain a 3-inch amplitude without fatigue or drop-off.

(a) During the last four years supplemental data have been obtained from this test by asking the patient, at the end of the fatigue curve, to make a special effort at the final squeeze. In the normal subject or the patient with myasthenia gravis, peripheral nerve or muscle impairment, this squeeze is generally no more than 10 per cent above the previous one. In patients with Parkinson's disease, where there is akinesia present, this final squeeze may be two to five times as high as the previous one (akinesia paradoxica) (5).

(b) By putting a gear shift into the motor that drives the ergograph it is possible to arrange it so that the patient squeezes the bulb every four seconds instead of every second. If the patient has fatigue from myasthenia or muscle disease this opportunity for a four-seconds' rest between every squeeze restores the fatigue curve towards normal. In Parkinson's disease, on the other hand, the presence of akinesia is not benefited by this period of rest and the amount of akinesia can be estimated from (a) and (b).

4). The conventional spring dynamometer is used in each hand with three consecutive squeezes, approximately one minute apart.

5). We also measure the time it takes the patient to remove his shoes and socks from each foot and put them back on again, tying the laces. Each element of this test, ten in all, is graphed on a sheet of paper. It has been determined that this task can be easily done by a normal person in between 35 to 45 seconds. In severe Parkinson's disease it is impossible to complete the test. Moderately advanced cases may take as long as three minutes.

6). We also measure the amount of tremor per minute of time, using a modified Eck Work Adder as a tremor recorder. If there is no Parkinson tremor the hand

resting on the apparatus produces no units on the electric counter and the tremor measurement is zero. If there is an extreme amount of Parkinsonian tremor the minute count may reach as high as 650.

In addition to these tests, performed by the specially trained nurse who sees all of our patients, the physician estimates on a 4-point scale the amount of rigidity in each wrist, elbow, ankle and knee, and the amount of tremor on each side of the body. All of this material is recorded on a single sheet at each visit of the patient. Since many patients will be seen four to six times in the course of a year, the presence of progression can be estimated with some accuracy by inspection of a series of these summarized ratings.

SUBJECTIVE MEASUREMENTS

For the past five years we have used a form which is reproduced in Figure 1. Though this can be mailed to the patient, we consider it more desirable to complete the form in interview with the patient, and in the presence, if possible, of a relative. There are ten sections calling for the patient to estimate the percentage of his ability to dress, undress, feed himself, etc. as compared to his state before the onset of the disease. Frequently this involves some discussion with the spouse; there may be differences between the estimates of the patient and his spouse, but these differences are usually no more than 10 per cent. In most intelligent patients the estimation of the handicap matches well with the objective deficit shown, say, by the shoe and stocking test described above. When the ten ratings are averaged they yield a fair subjective indication of the amount of disability the patient presents at that time.

As a check on their motor performance we also ask these patients to estimate the amount of help they require in these tasks. This is simply recorded at quartile points: "No help" (100 per cent independent); 25 per cent help (75 per cent independent); and so on. One would expect that the amount of help required should be a reciprocal of their ability to handle these activities, and indeed this is usually the case.

In 1958 we made a very careful analysis of 500 of these forms (2) that had been sent out to this number of patients, and found that they agreed significantly with the objective measurements previously described. An additional finding was a lack of correlation between the age of onset of the disease and the number of years the patients had been afflicted. It was found in this survey that only 20 per cent of the 500 patients had scores from 0 to 20 per cent, *i.e.* were completely incapacitated. Thirty per cent were between 80 and 100 per cent of normal, and were completely independent; and another 20 per cent had scores between 60 and 80 per cent, being thus only slightly dependent. This was a happier yield than we had anticipated, and indicated that there were large numbers of patients in whom progression had obviously not occurred very rapidly.

RESULTS

With these objective and subjective measurements before us we have found that 10 per cent of our patients are in the first degree of progression (Grade 1—Slight); 25 per cent are in Grade 2—Mild; 25 per cent are in Grade 3—Moderate; 20 per cent are in Grade 4—Considerable; and 20 per cent are in Grade 5—Rapid.

CASE EXAMPLES

Case 1. A 60-year old physics professor at a woman's college was first seen in 1946 because he had a subjective twitching of the muscle of his right thumb and a feeling of stiffness in the fingers. No true rigidity was encountered on examination. There was twitching in the individual muscle but this did not suggest any type of tremor. The electromyogram done on the adductor pollicis had a regularity of discharge suggestive of a Parkinsonian tremor, namely four per second. There were no other abnormal findings at that time. In fact, facial expression, gait and associated movements were all within normal limits. The diagnosis of this disease was not certain at that time, and no

treatment was advised. Twelve years later, after a year of travel and lecturing, he complained of the same symptoms to his local doctor, who noted a slight masking of the right side of the face, a little slowness of finger movements, and occasional twitching of the thumb. The physician thought the possibility of Parkinson's disease had to be considered. Artane was recommended, 2 milligrams three times a day. As a result of this medication the patient complained of being dull. He had some difficulty with his memory and some trouble focusing his eyes. There was some slight impairment in chewing and swallowing. Because of the difficulty with his memory and visual complaints he was once more referred for a complete study. He was taken off the Artane. The memory difficulty and dryness of mouth disappeared. The twitching of the right thumb muscle was studied with the electromyograph and was very much the same as it had been 12 years before. It was now certain that there was a slight masking of the right face and a very mild degree of Parkinsonism, but the progression was probably one of the slowest of anyone in our series. No other signs were found and this patient remains completely independent and 95 per cent of normal in all motor activities.

Case 2. This is a 42-year old woman, married and with two children, who first noted symptoms in 1934. These consisted of oculogyric crises and occurred about five or six times a week. They were not considered a symptom of Parkinsonism. About six years later the patient first noted a slight awkwardness and stiffness in the left hand. This did not bother her, since she was right-handed. Two years later there was a definite tremor and the diagnosis of Parkinson's disease was now established. She was first seen by the writer in 1951, at which time there was two plus tremor and one plus rigidity on the left side, loss of associated movements, and crises were still present. No symptoms of tremor or rigidity were present on the right or dominant side. Motor performance was normal on both sides. She was completely independent and able to look after her home and children without difficulty. In 1959 there was some progression but it had not spread to the dominant right side. She is now considering the advisability of having neurosurgical intervention. There has been some progression since 1949 but the process has not spread to the other side. She is still 95 per cent of normal in all of her usual activities and completely independent. The amount of rigidity and tremor in her left arm has definitely increased and progression would be regarded as mild. The annoyance and embarrassment of the tremor when in public is her primary concern, and it is understandable that she has been reluctant to take the risk of surgery because of her ability to lead an otherwise normal life.

Case 3. A 49-year old business executive first noticed a tremor in his left hand in 1940; by 1945 there was a Grade 2 tremor in this arm and some rigidity. Medication did not help. He was able to do all of his business work without difficulty and with complete independence. He had no impairment. He was first seen by the writer in 1958, 18 years after the onset of the disease. There were no symptoms whatsoever on the right or dominant side; some awkwardness in finger movements of the left hand with a four plus tremor and two plus rigidity. Some impairment of the ergograph was noted. No akinesia was present. Tremor registered 425 units per minute on the recorder. The patient's subjective estimate of his disability was 85 per cent of normal. This man was subjected to a right globus pallidus by I.C. and was seen fourteen months later. At this time there was no discernible tremor in the left hand, even when under artificial stress. There was no rigidity. His estimated that he was functioning 100 per cent normally. He was not taking any medication at that time. This case certainly represents mild progression during the first 18 years of the disease, together with a remarkably good surgical result (seen as negative progression in the year following the operation).

Case 4. This married female noted stiffness and tremor in her right arm in 1957. About three months later there was marked stiffness of the right leg. Three months later some tremor in the left arm appeared, and by the end of the year her gait was markedly impaired. There was deformity of both the right hand, right foot. When seen by us 18 months after onset she had great difficulty in moving about, although she was able to dress herself. Her subjective estimate of her normality was 60 per cent. Her rigidity was four plus on the right and three plus on the left. Tremor was 400 units per minute on the right and 200 on the left. This patient represents an extremely rapid case of progression (Grade 5).

Case 5. A 54-year old photostat operator first noted rigidity of his left leg in 1956. By 1957 there was also some rigidity of the left arm. Six months later a tremor developed in his left hand; when seen in 1958 he showed two plus rigidity on the entire left side and one plus tremor, registering 50 units on the recording apparatus. He was adjudged 75 per cent of normal, and completely independent. A right sided globus pallidus lesion was made, which produced a complication of

Mark X in appropriate square for each of the 10 items. Please enter under the 10 items your estimate of percentage of normal these ordinary acts of daily living, compared with the state you were in before you had Parkinson's disease. Have friends or relatives these categories. 100% is normal in every way in this category, so that you are no different from anyone else who does not have Par the value of 60–70% of normal. Indicate on right of sheet in appropriate column the amount of help you require in the 7 items.

Item	%	0	10	20	30	40	50	60	70	80	90	100%	Help Needed				100%
													0	25	50	75	
1. Dressing: putting on or taking off overcoats, clothes, stockings, socks, handling of buttons, zippers, shoe laces.										A	a		a A				
2. Washing: bathing, showers, drying, combing of hair, toothbrushing, shaving, urination, moving of bowels, wiping.										a	A		a A				
3. Eating: using spoons, forks, knives, cutting meat, buttering bread, drinking from glasses, chewing, swallowing, controlling spilling. Eating with others.										a A			a A				
4. Retiring: getting in and out of bed, turning over, getting comfortable, keeping covered.											a A		a A				
5. Indoor Activities: getting in and out of chair, opening and closing doors, up and downstairs, handling books on shelves, reading, turning pages, cards, other games, TV or radio knobs, writing.											a A		a A				
6. Outdoor Activities: walking, crossing street, moving with crowds, handling of swinging doors, avoiding obstacles such as stones in path and uneven ground.										a	A		a A				
7. Travel: getting in and out of auto, driving own car, getting in and out of busses, trains, planes, moving in aisles.											a A		a A				
8. Social: willingness to go calling, seeing friends or having friends at home. Movies, theatre, public entertainment, sports events, being seen in public at meetings, clubs. Conversation, being understood, voice.										A	a						
9. Business and Occupation: keeping up with job, value to organization. If still working, ability to keep up to normal. Hobbies, recreation. Ability to do house work, chores, bedmaking, cooking, dish-washing, sewing, cleaning up. Note if retired.										A	a						
10. Personal Morale: presence of discouragement and depression, avoiding contact with others. Amount of determination to adjust to this illness.											a A						

FIG. 1. Rating form used for patients' subjective ratings (see text). Ratings a and A repre-
1959. Patient was completely independent in 1954 and in 1959. Ratings a obtained in June,
an average per cent of normal of 86. These assessments substantiated results of objective
Ratings b and B represent appraisal of a 60-year-old patient who showed a rapid pro-
in 1955. Ratings b obtained in April, 1952, with an average per cent of normal of 80.
also supported the neurologic findings.

hemiparesis on the left side. Over a period of eight months with physiotherapy this slowly disappeared but a very definite amount of rigidity has now developed over the right arm and right leg. In December, 1959, this patient's subjective motor performance had reached the same level that it was in 1957, namely 65 per cent of normal. He represents a moderately severe progression (Grade 4) and was helped by surgical intervention.

Case 6. At the age of 49 this patient noticed a slowness of his right dominant side without

and amount of help needed now. The percentages of normal should be based on the difference between the present ability to do help you in this. From 0 to 10% represents such severe incapacity that you are essentially a total invalid, unable to do anything in Parkinson's disease. Please keep in mind that if you take twice as long as a normal person but *do it yourself without assistance* it represents

Item	%	0	10	20	30	40	50	60	70	80	90	100%	Help Needed				100%
													0	25	50	75	
1. Dressing: putting on or taking off overcoats, clothes, stockings, socks, handling of buttons, zippers, shoe laces.				B						b				b			B
2. Washing: bathing, showers, drying, combing of hair, toothbrushing, shaving, urination, moving of bowels, wiping.		B								b			b				B
3. Eating: using spoons, forks, knives, cutting meat, buttering bread, drinking from glasses, chewing, swallowing, controlling spilling. Eating with others.				B							b		b			B	
4. Retiring: getting in and out of bed turning over, getting comfortable, keeping covered.		B									b		b				B
5. Indoor Activities: getting in and out of chair, opening and closing doors, up and downstairs, handling books on shelves, reading, turning pages, cards, other games, TV or radio knobs, writing.				B					b					b			B
6. Outdoor Activities: walking, crossing street, moving with crowds, handling of swinging doors, avoiding obstacles such as stones in path and uneven ground.		B						b						b		B	
7. Travel: getting in and out of auto, driving own car, getting in and out of busses, trains, planes, moving in aisles.			B					b						b			B
8. Social: willingness to go calling, seeing friends or having friends at home. Movies, theatre, public entertainment, sports events, being seen in public at meetings, clubs. Conversation, being understood, voice.			B								b						
9. Business and Occupation: keeping up with job, value to organization. If still working, ability to keep up to normal. Hobbies, recreation. Ability to do house work, chores, bedmaking, cooking, dish-washing, sewing, cleaning up. Note if retired.			B						b								
10. Personal Morale: presence of discouragement and depression, avoiding contact with others. Amount of determination to adjust to this illness.							B				b						

sent appraisal of a 46-year-old patient who showed almost no progression between 1954 and 1954, with an average per cent of normal of 87; ratings A obtained in October, 1959, with neurologic examination and motor tests.
gression from 1953 to 1955. Patient was slightly dependent in 1952; completely dependent Ratings B obtained in August, 1955, with an average per cent of normal of 14. These ratings

tremor. He found writing and filing papers, and driving his car, very difficult within three months of the onset of symptoms. A year after onset there was difficulty in being understood; his voice had a tendency to fade to inaudible levels. While the diagnosis of Parkinson's disease was obvious, the patient and his family were not informed of it and treatment was not instituted. Four years after onset the other side became stiff and awkward. At this time the patient had reached a level of 60 per cent of normal and 25 per cent dependent. Disability was most marked in his virtually in-

audible speech. A variety of drugs was tried, and only partial help resulted from some of the analeptics. During the next three years there was a slow and steady deterioration. He became unable to dress or feed himself, could not turn over in bed, nor get out of a chair. Drooling became an embarrassment to his family and he had difficulty controlling his bladder. Eight years after onset he was placed in a nursing home. At that time he was no more than 20 per cent of normal and, of course, completely dependent. There was only slight tremor in the right hand and two plus rigidity on each side. Akinesia was as marked as we have ever seen on both sides. Nine years after onset he developed a terminal and fatal intestinal obstruction and died. This patient represents a type of Grade 4 progression that slowly, steadily, and relentlessly went on without any remissions and ultimately produced a complete incapacity.

Case 7. An insurance executive at the age of 46 noted a tremor of his dominant right hand and some dragging of his right foot shortly afterwards. At the end of a year the diagnosis of Parkinson's disease was confirmed and the patient was on medication (Artane) with a fairly good result. Over the next three years the disease progressed steadily, and symptoms, both tremor and rigidity, began to appear on the left side. He responded favorably to a mixture of Parsidol, Artane and Dexedrine. Five years after onset the stiffness and tremor on the right side was sufficiently disabling, in spite of his response to medication, so that he had difficulty in conducting his business affairs. He was still able to dress himself and go to work with about 20 per cent dependency. At that time he had a left-sided surgical lesion in the thalamus which reduced the tremor and rigidity on the right considerably, but produced a speech impairment as a side effect. For a period of nearly a year after the surgery he was generally improved in spite of the speech difficulty, and able to do considerably more, getting around and attending to his business. The disease steadily progressed on the left or non-operated side, however, and necessitated resumption of his medication at about the same level as preoperatively. Eighteen months after surgery (and six and one-half years after the onset of the disease) he was sent to us for an opinion as to whether bilateral operation was advisable. In order to ascertain this all medication was withdrawn. Thirty-six hours later there was some tremor and rigidity on the operated side which had not been apparent when he was on medication. There was a marked (four plus) rigidity and three plus tremor on the non-operated side and marked akinesia on both sides. The patient was quite unable to feed or dress himself. He was put back on medication and this improved his level to that on entrance to the hospital.

It was our opinion that the presence of akinesia and the marked degree of his disease on both sides, even though he had surgery, made a further surgical intervention unwise and too great a risk. It was also obvious that the extent of progression had been considerably masked by the successful effect of the drugs. This patient was indeed far more handicapped when he was off his medication than when taking it. He represents a Grade 4 progression, steadily involving both sides, with a satisfactory relief by surgery on one side and a fairly satisfactory result of medication as well. It is probably true that the prognosis in this case is poor, since further progression can certainly be anticipated involving both sides, and the presence of akinesia bilaterally is a very bad sign in this particular patient.

Case 8. A 63-year old business executive first noted a tremor in his left arm at the age of fifty. There was a very slow progression and not until five years later was rigidity of his left leg and arm, with some dragging of his foot, present. He obtained fairly satisfactory relief of the rigidity with Kemadrin and Thephorin. However, the tremor progressed and did not respond satisfactorily to these drugs; Parsidol accordingly was added to his schedule. There was no involvement of his right side. Twelve years after onset, when he was 62, a very slight amount of tremor was noticed in his right side. The tremor on the left was so disturbing that the patient was not satisfied with his medical therapy. He had continued to work in his store, carried a large number of responsibilities, and was concerned for the future. He was taking as much medicine as he could tolerate without side effects (Kemadrin, Thephorin and Parsidol). In April, 1959, arrangements were made for him to be seen in consultation by a neurosurgeon for the purpose of making a right-sided thalamic lesion. In July, 1959, he had a moderately severe coronary occlusion; was in bed for six weeks and made a satisfactory recovery. During this time he unburdened himself from his business affairs completely and went into total retirement. He also underwent a very healthy and somewhat unusual adaptation to his chronic illness so that minor irritations and worries were no longer bothersome. His only interests were to maintain his health, relax, and spend pleasant hours with his wife to whom he was intensely devoted. After a rest of three months in Florida he was seen in December 1959. The tremor on the left side was definitely less than it had been six months previously. On the right it could only be brought out under stress. Rigidity on the left

side was completely controlled on smaller amounts of medication than he had previously taken. All plans for neurosurgical intervention were abandoned. The patient stated he felt quite happy about being 30 per cent dependent, spending his summers in New England, and his winters in Florida. He had adapted to his coronary disease restrictions in an extraordinarily efficient manner. He explained this by saying that during his weeks of enforced bed rest he had altered his philosophy of life considerably. He now wished to live in comfort, in a relaxed state for as long as he could. He had no interest whatever in the further competitive acquisition of wealth. If he had a surgical lesion and had reached this level of improvement one might have been reasonably satisfied. Surely nobody recommends a coronary occlusion as a successful therapeutic attack on Parkinson's disease. In this case, however, prognosis was certainly altered by the presence of this cardiac complication and it would seem, at least for the present, that the rate of progression has been slowed. This patient would be regarded as an example of Grade 3 progression.

DISCUSSION

In 1952 Markovich and Schwab (3) reported on prognosis and progression in Parkinson's disease in 65 patients who had been examined over a period of three years. At that time we felt that an easy-going, rather placid personality showed the slowest progression, and those driving, competitive personalities, as well as the vulnerable weak personality, progressed more rapidly. There was some evidence found that patients who had vascular disease, such as hypertension or generalized arteriosclerosis, seemed to progress more rapidly than those without vascular disorders. In this smaller group we could find no evidence that the type of Parkinson disease, *i.e.* postencephalitic or idiopathic, had any relevance, nor was there any correlation with the age of onset, sex, or length of time that the disease was present.

Recently we have evaluated the distribution of our present number of patients according to age of onset. The modal decade for onset of the disease is the sixth—between the ages of 51 and 60. About 35 per cent of all of our living patients, in number 700, experienced the onset of the disease in this decade. Sixty-five per cent of this sample had an onset between the ages of 40 and 70. We have found that 40 of our patients have survived from 25 to 29 years since the onset of their Parkinsonism, *i.e.* their progression has been exceedingly slow; one-half of this number, surprisingly, are completely independent. In the older group of patients, those whose onset was after the age of 60, the average survival is nine years, and in this group 60 per cent are still completely independent. We have, then, again found no correlation with prognosis or progression in relation to age of onset or duration of the disease. Examples have been shown of patients with mild unilateral symptoms that have persisted for several decades. On the other hand, some patients, whether in their 40's or 60's, have rapid and steady progression from the onset and become disabled within several years. There still seems to be some relation between the degree of progression and the individual adaptiveness and strength of personality. Certainly the presence of other physical disease such as hypertension, generalized arterioscleorisis or diabetes, contributes to the rapidity of progression and reduces the chances of a favorable prognosis. Severe trauma or prolonged stress usually aggravates the symptoms of Parkinson's disease and in about 50 per cent of the cases this aggravation seems to persist for reasons that are not understood.

We have found that early evidence of akinesia is a poor prognostic sign and is usually associated with a more rapid progression of the disease. When the disease becomes bilateral during the first year it seems that progression is more rapid and the prognosis less favorable. The long persistence of a unilateral Parkinsonism, in general, is a good prognostic sign and is associated with slow progression. Progression does not appear to be differentially related to tremor or rigidity as an initial symptom, although rigidity is clearly more

disabling than tremor. It is apparent from this study that early involvement of speech, which is usually associated with akinesia, is related to rapid progression of the symptoms and a poor prognosis. Early involvement of memory and loss of intellectual functions, marked changes in personality and loss of drive and ability to complete tasks and to initiate them (these are related to the motor akinesia) are signs also associated with rapid progression and a poor prognosis.

It is obvious that the factors accelerating progression in Parkinson's disease are far from well understood. There is some evidence that the presence of other diseases and certain symptoms such as akinesia are associated with a less favorable prognosis. Certainly it must be kept in mind that there are a number of patients with unilateral symptoms of the disease who have an exceedingly slow course with a good prognosis. It is unjustified at the present time to group all patients with this disease in one category and to assume a steady, relentless and rapid progression and poor prognosis.

SUMMARY

Most patients with Parkinson's disease have some steady progression of the symptoms and it is unusual to have the disease remain in a fixed state for many years. The degree of progression varies tremendously from patient to patient and the prognosis is, therefore, variable as well. In some patients who have unilateral disease, progression is exceedingly slow and prognosis is good. In others who within the first year develop bilateral signs, particularly with akinesia, progression is usually rapid and the prognosis is poor. Certain clinical findings have been related to these variables. No definitive pattern can be established at the present time, for our knowledge of the mechanism of these differences in progression is not understood.

REFERENCES

1. Baker, A. B. *Clinical Neurology*, p. 1151. Hoeber-Harper, New York, 1955.
2. England, A. C. and Schwab, R. S. The management of Parkinson's disease. A.M.A. Arch. Int. Med., **104**: 439–468, 1959.
3. Markovich, S. and Schwab, R. S. Prognosis and progression in Parkinson's disease in patients under medical treatment. Arch. Internat. Studies Neurol., **2**: 1–9, 1952.
4. Miller, H. Parkinson's disease. Brit. Med. J., **2**: 158, 1954.
5. Schwab, R. S., England, A. C. and Peterson, E. Akinesia in Parkinson's disease. Neurology, **9**: 65–72, 1959.
6. Wechsler, I. *Clinical Neurology*. 8th ed. Saunders, Phila., 1958.

MÉNIÈRE'S SYNDROME OR AURAL VERTIGO: SURGICAL THERAPY[1]

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There is no doubt that vertigo is one of the most discommoding and distressing conditions to which a person may be subjected. Consider one's surroundings whirling around so violently that one crashes to the floor. Even when lying down, merely opening one's eyes may bring on another sickening whirl. To have suffered seasickness is to have tasted the hors d'oeuvres of vertigo.

Vertigo implies the sensation of spatial turning, whirling or rotation and as such must be distinguished from dizziness and lightheadedness, which are characterized by a faintness, unsteadiness, lack of balance or blackout. These conditions, although at times disabling to the patient, will be dismissed from this discussion without further comment.

This discussion of aural vertigo or Ménière's syndrome is largely based upon a series of 30 patients who had a partial eighth cranial nerve section. It is, therefore, not a representative sample of patients suffering from this condition, for the majority do not have symptoms of such severity or frequency that they are referred to a surgeon. On the other hand it seems probable that the series is not contaminated by patients with other conditions resembling the milder forms of aural vertigo.

GENERAL INCIDENCE AND PATHOGENESIS

It is of interest that an ethnic factor, and perhaps the diet of the individual may be important in the development of Ménière's disease. Only one patient in this series of 30 cases was of other than Caucasian stock. The senior author has noted that in the Orient, Ménière's disease is quite rare. Although the diet of the patients in this series was not unlike that of the average American family, it may be noteworthy that in all cases in which the question was posed, the patients admitted a liking for highly seasoned foods. In no case did the patient state that unseasoned food was preferred.

The sex of the patient is apparently not an important factor in pathogenesis; approximately half of the patients were male and half female. There does not seem to be a predilection for one ear to be more frequently affected than the other, although in this series 12 patients had involvement of the right ear and 18 the left. Other reports show no significant difference between the incidence on the two sides.

At the time of onset of symptoms of Ménière's syndrome most people are in their third to fifth decades of life (Table 1).

Factors precipitating Ménière's syndrome are not at all consistent. In this series many conditions were said to have preceded the onset of the trouble: severe headache, swimming, extraction of teeth, influenza, spinal anesthesia, peptic ulcer and noisy environment were among the many factors mentioned. In six patients there was a history of allergy and in three a history of hay fever. In ten patients some operative procedure had been carried out within a few years of the onset of the symptoms; various other conditions were noted in the antecedent personal history but none seemed to have definite bearing upon the onset of Ménière's syndrome. Although inquiry elicited a family history of diabetes in four cases, a hy-

[1] It is a pleasure to dedicate this paper to Dr. Ernest A. Spiegel, whose studies have elucidated many of the aural functions. We hope that Dr. Spiegel may have many future years to devote to the unravelling of the mysteries of the nervous system.

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TABLE 1
Age Distribution

Age in Years	At Onset of Symptoms	At Operation
1–19.9	0	0
20–29.9	7	1
30–39.9	8	8
40–49.9	8	10
50–59.9	5	7
60–69.9	2	4
	30	30

pertensive tendency in four and allergic manifestations in three, no causal relationship between any hereditary trait and Ménière's syndrome could be established.

SYMPTOMATOLOGY

The cardinal symptoms of Ménière's syndrome form a triad of vertigo, tinnitus and deafness.

Vertigo. A true vertigo implies a sensation of rotation either of the individual or his environment. In most patients vertigo occurs with the initial attack, but in a few a sensation of dizziness precedes the paroxysmal spells. Usually the attack strikes suddenly, but occasionally certain prodromata may warn of the approaching crisis. For a few minutes or as long as an hour, the patient may note an increase in the tinnitus and deafness of the affected ear, at times associated with paresthesias of the face, head or arm on the involved side. In about 10 per cent of patients there is some impairment of consciousness with the sudden vertigo or "swoop of the hawk." With the onset of severe vertigo, the patient's head whirls and his environment jumps about in such a disconcerting fashion that he must lie down or be thrown to the floor, occasionally with such force as to sustain skeletal fractures. As an intense nausea develops, the patient vomits profusely and frequently, especially on movement of the head. The vertigo may last for only a few minutes or may persist for hours or days. It abates gradually, leaving the individual with a feeling of unsteadiness, which is aggravated by change in position of the head. The vertiginous attacks recur at intervals, sometimes of days but more frequently of months. Although patients do complain of some interictal dizziness and unsteadiness, this is not a cardinal symptom.

Tinnitus. Usually the tinnitus of Ménière's syndrome is unilateral or predominantly in one ear. It has been described in many different terms, as hissing, roaring, swishing, buzzing, ringing, beating or vibrating. However, the most common term employed is "buzzing" or "roaring." The pitch and intensity of this noise may be of any magnitude and may vary from time to time in the same patient. The tinnitus may precede other manifestations of the disorder by years or may appear with the first attack of vertigo. It tends to increase in the involved ear just before the time of or after an acute attack. This characteristic effect may indicate the ear responsible when tinnitus is bilateral.

Deafness. Deafness, the third cardinal symptom, is usually unilateral and on the side of the tinnitus, but occasionally may involve both ears. The onset is often gradual and frequently unnoticed, but may occur suddenly with tinnitus. The deafness may be aggravated by the acute vertiginous attacks and, in fact, may be noted only after such attacks.

The impairment of hearing in Ménière's syndrome has certain typical characteristics, as Lindsay (21) and Walsh (33) emphasize. In the early stage of the condition, patients hear quite well at times and poorly at other times, having a swing of 20, 30 or even 40 decibles in their auditory acuity. Often the period of impaired hearing precedes or follows a vertiginous episode. Walsh (33) thought that there was a relatively greater loss in the low than high tone range in the early stages of Ménière's syndrome. As the disease progresses the curve tends to become flattened and eventually in

long-standing cases the appreciation of high tones is lost. Williams (35) also noted the tendency for a decrease in the low tone range, although he recognized that any type of audiogram may be found in Ménière's syndrome. The preoperative audiographic findings in this series differed greatly. Some five patients had more impairment of low than high tones; 15 had a high tone loss and the remaining 11 patients practically a flat audiogram. Of the five patients with a low tone loss, four had symptoms for six years or less. Nine patients of the 15 having a falling off in the high tone range, had had symptoms for more than six years, and only six had had Ménière's syndrome for less than six years. These figures are compatible with Walsh's thesis regarding the audiographic findings in Ménière's syndrome.

In the present series vertigo was early associated with tinnitus in most cases, with impairment of hearing occurring later. Some patients, however, were not aware of an impairment of hearing until it was demonstrated by audiographic examinations. Some 14 patients had vertigo associated with tinnitus from the beginning of their episodes; three had vertigo alone for a time before tinnitus occurred, and nine had tinnitus as an isolated symptom before the onset of vertigo. In the three cases in which vertigo occurred initially, one patient developed tinnitus several years after the onset of vertigo and some years later noted impairment of hearing. In the second case the hearing became impaired shortly after the onset of vertigo, and tinnitus occurred about a year later. In the third patient the vertiginous attacks with nausea, vomiting, headache and weakness were present for about a week before tinnitus and loss of hearing were noted.

In the nine cases in which tinnitus preceded the vertigo, four patients had impairment of hearing at the time of the onset of tinnitus, and five had tinnitus without hearing impairment initially.

One must conclude, therefore, that the order of the onset of the three cardinal symptoms of Ménière's disease is quite variable, although statistically vertigo is apt to occur first, then tinnitus and finally hearing impairment.

DIFFERENTIAL DIAGNOSIS

When a person presents a complaint of true vertigo, the clinician is apt to think of four common conditions which give rise to this disconcerting sensation, *viz.* acute labyrinthitis, basilar insufficiency, acoustic neurinoma and Ménière's syndrome or aural vertigo. A good history will usually serve to confirm or rule out the possibility of one of these conditions.

Acute labyrinthitis. The patient with labyrinthitis has almost always but one acute attack, although the unsteadiness may persist for months. The acute episode usually coincides with evidences of general malaise, and in fact may be associated with symptoms of an acute grippe, gastrointestinal upset, respiratory upset or middle ear disease. The vertigo gradually increases in severity over a few hours and may be accompanied by nausea and occasionally vomiting. Diplopia may be present for a short time, often in association with nystagmus. The patient remains in bed, usually lying on the affected ear, for hours or days, until the vertigo gradually subsides, without residual, usually never to recur. However the complete return of balance may require as long as six months.

Basilar insufficiency. True vertigo may precede, initiate or be associated with thrombosis of the posterior inferior cerebellar artery. The characteristic findings of Wallenberg's syndrome within a day or so will confirm the diagnosis. Intermittent insufficiency of the basilar artery may be associated with vertigo of a temporary, and even momentary, nature. The sensation may be associated with confusion, diplopia, blurred vision, slurred speech, nausea and vomiting and evidences of long sensory and motor tracts. Recurrent attacks of this na-

ture raise the suspicion of basilar insufficiency.

Acoustic neurinoma. Although other tumors of the cerebello-pontine angle may be associated with vertigo, acoustic neurinomas are the most common neoplasms of that area to produce this symptom. The vertigo may occur before other symptoms or signs of the tumor but usually within a short time the vestibular function is found to be absent in the involved ear. Other evidence of damage to cerebello-pontine angle structures—facial hypalgesia, unilateral deafness, unsteadiness when walking and unilateral cerebellar dysfunction—usually occur early and confirm the diagnosis. In roentgenograms of the skull, the acoustic meatus on the involved side may be enlarged. If the spinal fluid is examined the protein is usually increased to 100 milligrams or more.

Other conditions. Rarely do other conditions cause paroxysmal vertigo. Multiple sclerosis may have vertiginous attacks as an early symptom. A fourth ventricle tumor occasionally is associated with vertigo. Epileptic attacks may be initiated by a sensation of rotation or whirling but the subsequent seizure will enable one to ascertain the true nature of the disturbance. Paroxysmal positional vertigo is an otologic diagnosis for brief episodes of labyrinthine disturbance when the head is held in certain positions. Nystagmus occurs after a few seconds and disappears with the cessation of the whirling sensation. Tinnitus and deafness do not occur. Whether this is a distinct entity or another example of pseudo-Ménière's syndrome—the atypical form of aural vertigo—is not yet established.

THE MEDICAL THERAPY OF MÉNIÈRE'S SYNDROME

The majority of patients afflicted with Ménière's syndrome respond to medicinal treatment. Cawthorne (4) reported that more than 50 per cent of patients were relieved by conservative treatment and another 25 per cent did not progress under medical management. Williams (35) stated that 80 per cent of patients were benefitted by medical treatment. However, there are some patients who do not respond to such conservative measures, or for one reason or another are unable to follow medical therapy. These are candidates for surgical procedures. There is, then, no competition between medical and surgical treatment, but rather a complementary relationship.

The patients in this series had tried at some time all forms of medical therapy recommended for Ménière's syndrome. Because anxiety states seemed to be related to the attacks, some patients had taken sedatives and been given psychotherapy. Phenobarbital was somewhat effective in two patients. Because, as Mygind and Dederding (25) pointed out, Ménière's disease may be due to alterations in capillary permeability resulting in a hydrops of the labyrinth, several patients had been prescribed a restriction of fluid intake and a low salt diet. Two patients found these measures effective for a time, but two other patients were not helped. Ammonium chloride (3 gm. t.i.d.) which was considered the most effective diuretic, was tried by four patients in association with other therapeutic regimes with temporary success in only one case. Potassium (as potassium nitrate, 15 grs. t.i.d.), which has been recommended to increase intracellular and decrease interstitial fluid, was tried by one patient with some initial success. Because calcium metabolism has been implicated as a factor in allergy, calcium chloride was prescribed without effect. Histamine, given intravenously, temporarily relieved six patients. Dramamine (50 mg. t.i.d.) was used in five cases with some relief. Nicotinic acid (100 mg. t.i.d.), which acts in somewhat the same way as histamine, was tried in five patients, two of whom obtained beneficial results. The various vitamin preparations were used in many instances with minimal effects.

SURGICAL TREATMENT

Two types of surgical therapy for Ménière's syndrome are now being carried out

—destructive labyrinthectomy and partial acoustic nerve section—as well as a number of less popular but nevertheless highly advocated procedures such as sympathectomy, chorda tympani section, etc. It is impossible to assess the value of these various procedures at the present time. When a series of a hundred cases has been followed for over two years with careful pre- and postoperative studies of hearing and vestibular function, a valid comparison may be made of the various methods. Because the remaining hearing in the involved ear may be preserved, partial section of the eighth nerve has been practiced from the relief of Ménière's syndrome.

This series is composed of 30 cases operated upon within the past 10 years without a death. Some 26 patients have been followed from one to 10 years; contact was lost with four after their period of hospitalization. Although the immediate postoperative course of these latter patients was satisfactory, their subsequent history is unknown.

OPERATIVE PROCEDURE

With the patient anesthetized, intubated, and lying on the side of the normal ear, a straight incision was made from a point 2 cm. posterior to and 3 cm. above the mastoid process inferiorly and posteriorly for a distance of 7 cm. The muscles were split or cut to expose the suboccipital surface of the occipital bone. The periosteum was separated from the bone, to expose the bone from the mastoid medially for about 5 cm. and from the superior nuchal line inferiorly for about 5 cm. The bone was perforated and the opening enlarged to a diameter of approximately 5 cm. The dura mater was opened by reflecting a small flap inferiorly. By slipping a narrow brain retractor medially the arachnoid over the cisterna magna may be ruptured and fluid allowed to escape. This maneuver allows the cerebellar hemisphere to fall away from the lateral wall and tentorium so that little retraction is necessary to bring into view the 9th, 10th and 11th nerves and the more rostrally situated acoustic nerve. This nerve usually appears as a white cord passing into the ceiling of the exposure. If carefully examined it is seen to be diveded into two parts by a groove in which a small vessel usually lies. This groove divides the acoustic nerve into an anterior one-half to two-thirds representing the vestibular portion of the nerve and a posterior auditory portion. With a straight sharp dissector the nerve is separated into anterior and posterior portions. The anterior part is then picked up on a right-angled hook and cut or coagulated. The facial nerve is hidden by the remaining auditory nerve.

The field is irrigated and the dura mater closed. The muscles are approximated in anatomical layers and the scalp margins brought together.

RESULTS

The clinical result, assessed some years after an operation, must be considered not only in terms of the primary disorder but of the total well-being of the patient. Within this frame of reference results cannot be expected to be as good as in a purely focal analysis, especially if one is dealing with an older group of patients. Accordingly some 15 patients are considered as 100 per cent results. They have had no vertigo or dizziness. Their hearing is not impaired over the preoperative condition and they have had no augmentation of their tinnitus. Six patients may be classified as 90–99 per cent successful, having no vertigo but occasionally feeling dizzy. Four are considered to be 70–89 per cent successful because of mild dizziness at times; two have never had vertiginous spells. One patient, considered as 50 per cent successful, has been very nervous and has occasional light-headed spells (Table 2).

The effect of the operation on the individual aspects of Ménière's syndrome should be examined.

Vertiginous attacks. Of the group of 26 patients, 24 have been completely relieved

TABLE 2

Preoperative Duration of Symptoms and Postoperative Appraisal

Result	Duration of Symptoms					
	Less than 1 year	1 to 2 years	2 to 5 years	5 to 10 years	More than 10 years	Totals
100% successful	2	6	3	0	4	15
90–99% successful	0	1	1	2	2	6
70–89% successful	0	0	2	1	1	4
50% successful	0	0	0	1	0	1
Total	2	7	6	4	7	26

TABLE 3

Vertigo and Dizziness One to 10 Years after Operation

Number of Cases	No Vertigo	Rare Vertigo	No Dizziness	Mild Dizziness	Occasional Dizzy Spells
26	24	2	18	3	5

TABLE 4

Postoperative Audiographic Findings of Differential Section of Eighth Nerve

No. Change	Slightly Impaired	High Tone Loss	Deaf	Total
10	3	6	2	21

of their vertiginous spells. Two patients were quite well until seven months and six years postoperatively, when they experienced a vertiginous spell (Table 3). The character of the spells before and after operation was the same in these two patients. Neither, however, has had sufficient trouble to warrant severing the nerve completely (Table 3).

For a while after operation most patients had some dizziness, nausea, vomiting and nystagmus, lasting about 10 days, but sometimes the dizziness persisted considerably longer. These sequelae in this series were rather slight, and precipitated usually by movement of the head or body. This dizziness cleared entirely in 18 patients, but three patients complained of occasional slight, momentary dizzy feelings when under nervous tension. Some five patients complained, at times, of a light-headed sinking feeling which occasionally was accompanied by sweating or nausea. These episodes, probably, should be considered abortive vertiginous attacks (Table 3).

Auditory acuity. In 28 cases a differential section of the vestibular portion of the 8th nerve was made and in two cases a complete section of the 8th nerve was made. In 27 cases of partial section on which data is available, 14 patients subjectively have unchanged or improved hearing, and the other 13 have decreased auditory acuity (Table 4).

Postoperative audiograms on 21 patients have demonstrated no change in hearing in 10 (Figure 1), slightly impaired audition in three (Figure 2), a loss in the high tone range in six (Figure 2) and complete deafness in two patients (Figure 3) (Table 4). These audiographic examinations were made a short time after operation and may not represent the permanent auditory state, for losses in the low or high tone range may disappear after some months. However, audiograms of irregular contour were obtained from patients more than one month after operation (Nos. 33, 25 and 20 in Figure 2).

With respect to the relation between relief of symptoms and postoperative hearing acuity, some 7 patients who were completely relieved of their spells had no hearing impairment audiographically even a short time after operation, and three other patients had no subjective hearing loss. In the other eight cases varying degrees of hearing loss were present. Of the nine patients who had spells of dizziness postoperatively, five had some hearing loss (Table 5). Of the 14 patients who had no change in hearing postoperatively, ten were relieved of their spells and dizziness; of the 13 cases who had some hearing loss following operation, eight were completely relieved of their spells and dizziness. Consequently from these observations

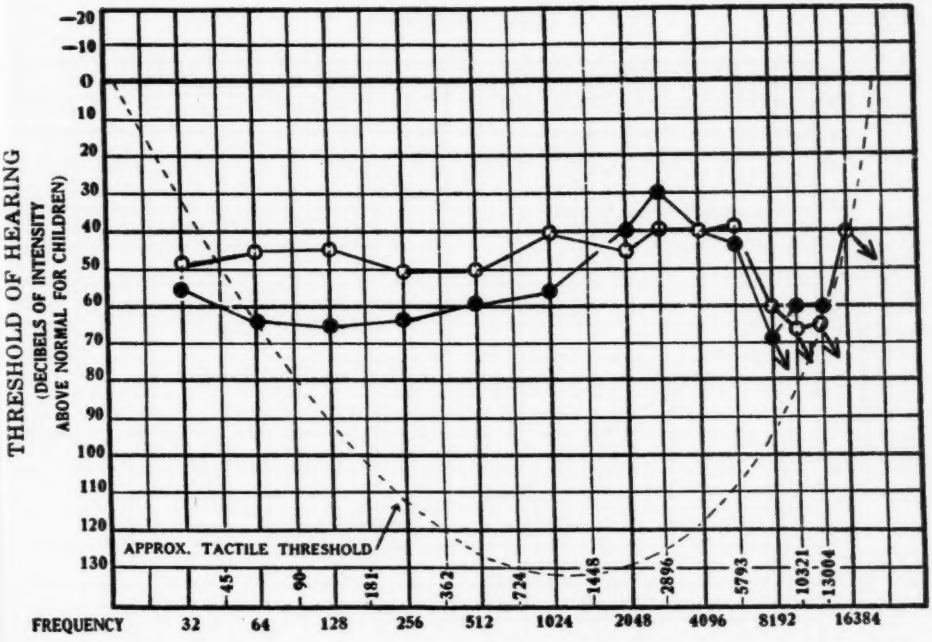

FIG. 1. (Case #12). Pre- and postoperative (10 days) audiograms representative of those of 11 patients (#9, 11, 12, 14, 16, 18, 19, 20, 24, 25, 32).

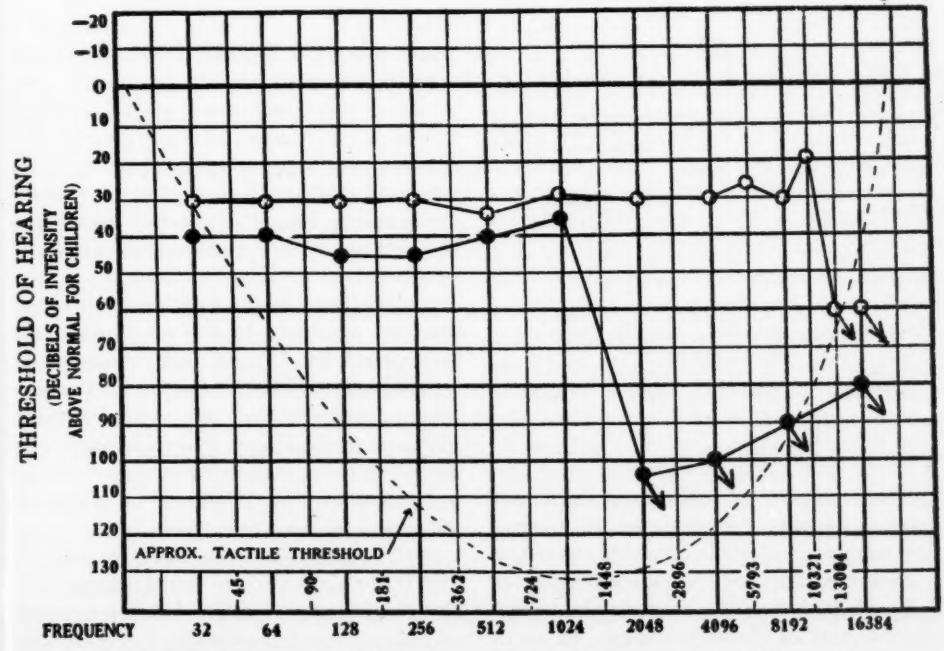

FIG. 2. (Case #2). Pre- and postoperative (8 days) audiograms representative of those of 5 patients (#2, 3, 6, 10, 17).

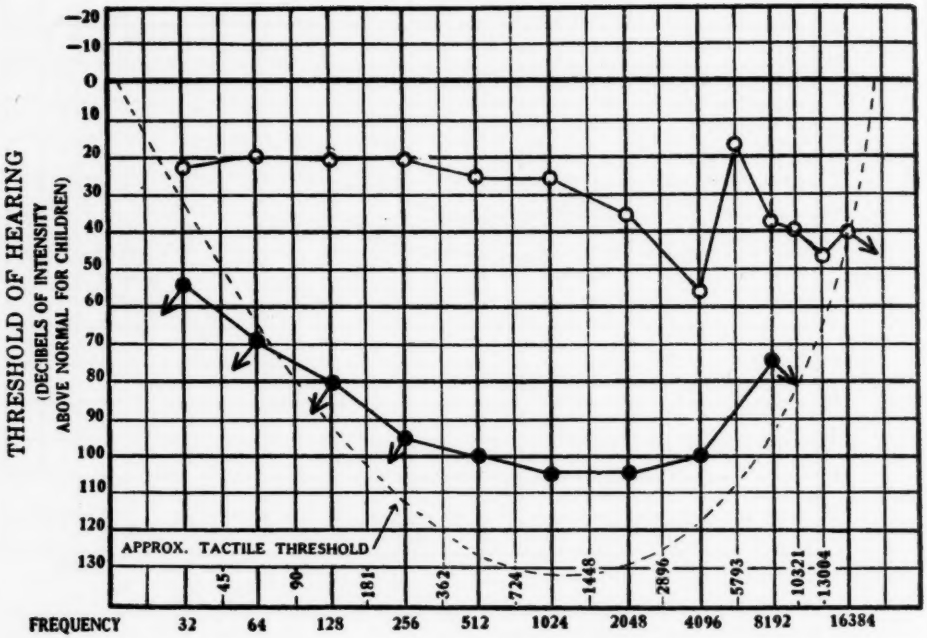

FIG. 3. (Case #1). Pre- and postoperative (13 days) audiograms representative of those of 5 patients (#1, 4, 7, 31, 34).

TABLE 5

Vertigo, Dizziness and Postoperative Hearing

	No Vertigo or Dizziness	Occasional Vertigo or Dizziness	Total
Hearing unchanged	10	4	14
Hearing worse	8	5	13
Total	18	9	27

TABLE 6

Tinnitus after Differential Section of the Eighth Nerve

No Tinnitus	Better	Same	Worse
6	13	8	2

we must conclude that there is no significant relation between preservation of hearing and recurrence of spells following operation.

Tinnitus. Relief of ringing occurred in six patients, including the two who had complete section of the eighth nerve. In all of these cases, the hearing was impaired to some degree after operation. In the 23 cases in which the tinnitus was known to have persisted after operation, 13 claimed the noises to be less, eight the same and two worse (Table 6). It is noteworthy that in every case in which the auditory acuity was not changed, some tinnitus was present postoperatively.

Unsteadiness. In the 29 patients on whom data are available, 12 had no unsteadiness postoperatively, 13 noted less but occasional unsteadiness, one had the same disturbance as preoperatively and the remaining three had more unsteadiness. The disturbance was described as a staggering in the dark or upon rapid turning. There was no ataxia on finger-nose or heel-knee tests.

Other neurological sequelae. No patient who had a section of the vestibular portion of the eighth nerve had involvement of other cranial nerves immediately following the

procedure, but three patients developed a facial palsy from ten days to six weeks after the operation. This cleared within a month in all three cases.

Relation between duration of the syndrome and the result. In Table 2 the duration of the symptoms is presented in terms of general results. No correlation is apparent: patients with both short and long histories have obtained good results.

DISCUSSION

The medical and surgical treatments of Ménière's disease, in general, are complementary. Most of the patients in this series had been treated medically unsuccessfully. Other forms of surgical treatment may be mentioned. Many reports in the literature indicate that cervical sympathectomy is effective in young or middle-aged people who have had symptoms only a short time. It is said to have a beneficial effect upon vertigo, to improve tinnitus and to decrease deafness to a variable degree. Section of the chorda tympani nerve is also said to produce these effects. Labyrinthotomy does stop vertiginous attacks, but usually destroys the hearing on the operated side. In spite of attempts to preserve the cochlear function by diathermy coagulation of the vestibular portion of the labyrinth, Day (9) found that this method was not selective. According to Guilford *et al.* (14), the operations designed to destroy the membranous labyrinth are not entirely satisfactory. Cauterization or chemical destruction with alcohol may cause facial paralysis and removal of the membranous horizontal semicircular canal may abolish the symptoms only temporarily. After complete destruction of the vestibular sense organs by removal of the contents of the vestibule as well as the horizontal anterior vertical membranous canals, as carried out by Lindsay and Siedentop (22) and Guilford (14), vertigo was controlled, tinnitus markedly improved and all hearing, distorted and normal, in the involved ear lost. Therefore, for patients suffering from Ménière's syndrome with severe impairment of hearing on the involved side, such a procedure may be recommended, but a better intervention for patients with useful hearing in the involved ear would be an operation which preserves the hearing, such as an intracranial differential section of the eighth nerve. According to Green and Douglass (13), who reported on Dandy's series, partial section of the eighth nerve will relieve vertigo, although after partial section some patients continue to have attacks which may be eliminated by a subsequent total section. This would correlate with our observation that some vestibular function persists after partial section, probably due, as Rasmussen demonstrated, to the intermingling of a considerable number of vestibular with cochlear fibers of the eighth nerve. However, some persistent vestibular function is not incompatible with a good result, for two patients in this series with some remaining vestibular response have gone eight years without an attack. It would seem that if most of the impulses from the vestibular end organ are abolished, the symptoms of Ménière's disease can be cured in most cases with preservation of hearing. Several writers have reported similar results. Cawthorne's (3) experience with patients at the National Hospital, Queen Square, indicated that in most cases hearing was spared. There may be no correlation between preservation of hearing and recurrence of spells or dizziness. Postoperative disappearance of tinnitus usually parallels the loss of hearing. In every patient in this series having no hearing loss postoperatively, some tinnitus remained. In Dandy's series only 26.8 per cent of patients were free from tinnitus after section of the vestibular nerve (13). Whether other operations such as sympathectomy, even in early cases, will permanently eliminate or modify tinnitus remains to be proved.

SUMMARY

The diagnosis and medical therapy of Ménière's syndrome are discussed.

A series of 30 cases of Ménière's syndrome was treated by intracranial section of the vestibular nerve without a death.

The vertiginous attacks were eliminated in all but four cases, in two of which isolated spells occurred at seven months and six years respectively after operation, and in the other two very mild attacks continued postoperatively.

The relief of tinnitus was associated with an increased impairment of hearing; elimination of the vertigo, however, did not show this relationship.

REFERENCES

1. Aring, C. D., Ryder, H. W., Roseman, E., Rosenbaum, M. and Ferris, E. B. Effect of nicotinic acid and related substances on the intracranial blood flow of man. Arch. Neurol. & Psychiat., **46:** 649–653, 1941.
2. Cawthorne, T. Some observations of the pathology and surgical treatment of labyrinthine vertigo of non-infective origins. An Hunterian Lecture delivered at the Royal College of Surgeons, England. Ann. Roy. Coll. Surgeons England, **4:** 342–359, 1949.
3. Cawthorne, T. Ménière's disease. Discussion. Proc. Roy. Soc. Med., **43:** 289–290, 1950.
4. Cawthorne, T. Ménière's disease. Discussion. J. Laryng. & Otol., **70:** 695–706, 1956.
5. Crowe, S. J. Ménière's symptom complex: A study based on examinations made before and after intracranial division of the vestibular nerve. Medicine, **17:** 1–36, 1938.
6. Dandy, W. E. Aural vertigo; Treatment of section of only the vestibular portion of the acoustic nerve. Bull. Johns Hopkins Hosp., **53:** 52–55, 1933.
7. Dandy, W. E. Ménière's disease: diagnosis and treatment. Report of thirty cases. Am. J. Surg. **20:** 693–698, 1933.
8. Dandy, W. E. Aural vertigo in a deaf mute. Arch. Surg., **50:** 74–76, 1945.
9. Day, K. Labyrinth surgery for Ménière's disease. Laryngoscope, **53:** 617–630, 1943.
10. Dedering, D. Our Ménière treatment (principles and results). Acta oto-laryng., **16:** 404–415, 1931.
11. Dix, M. R. Conservative surgery in the management of Ménière's disease. J. Laryng. & Otol., **70:** 686–694, 1956.
12. Frenckner, P. Some viewpoints on operative treatment in Ménière's disease. A. M. A. Arch. Otolaryng., **55:** 420–433, 1952.
13. Green, R. E. and Douglass, C. C. Intracranial division of the eight nerve for Ménière's disease. Ann. Otol. Rhin. & Laryng., **60:** 610–620, 1951.
14. Guilford, F. R., Wright, W. K. and Draper, W. L. Surgical treatment of Ménière's disease. South. M. J., **50:** 178–182, 1957.
15. Hall, I. S. Discussion. Proc. Roy. Soc. Med., **43:** 289, 1950.
16. Harrison, M. S. Conservative surgery in the management of Ménière's disease. J. Laryng. & Otol., **70:** 680–685, 1956.
17. Keith, N. M. and Binger, M. W. Diuretic action of potassium salts. J. A. M. A., **105:** 1584–1591, 1935.
18. Keith, N. M., Osterberg, A. E. and Binger, M. W. The effect of certain potassium salts on acid base excretion in the normal individual. Am. J. Physiol., **119:** 347–348, 1937.
19. Kern, R. A. The role of water balance in the clinical manifestations of allergy. Am. J. M. Sc., **199:** 778–789, 1940.
20. Lewis, R. S. Conservative surgery in the management of Ménière's disease. J. Laryng. & Otol., **70:** 673–679, 1956.
21. Lindsay, J. R. Symposium. Ménière's disease. Pathology. Tr. Am. Acad. Ophth., **60:** 172–176, 1956.
22. Lindsay, J. R. and Siedentop, K. H. Labyrinthine surgery in the treatment of Ménière's disease. Ann. Otol. Rhin. & Laryng., **64:** 69–78, 1955.
23. McKenzie, K. G. Intracranial division of the vestibular portion of the auditory nerve for Ménière's disease. Canad. M. A. J., **34:** 369–381, 1936.
24. Marmorston-Gottesman, J. and Gottesman, J. The use of histamine as a standard test for diminished resistance in suprarenalectomized rats. J. Exper. Med., **47:** 503–514, 1928.
25. Myging, S. H. and Dederding, D. Ménière's disease as an indicator of disturbances in the water metabolism, capillary function and body condition. Ann. Otol. Rhin. & Laryng., **47:** 55–62, 1938.
26. Myging, S. H. and Dederding, D. II. Clinical experiments with reference to the influence of the water metabolism on the ear. Ann. Otol. Rhin. & Laryng., **47:** 360–369, 1938.
27. Myging, S. H. and Dederding, D. III. The diagnosis and treatment of Ménière's disease. Ann. Otol. Rhin. & Laryng., **47:** 768–774, 1938.
28. Popkin, R. J. Nicotinic acid: Its action on the peripheral vascular system. Am. Heart J., **18:** 697–704, 1939.
29. Rasmussen, A. T. Studies of the VIIIth cranial nerve of man. Laryngscope, **50:** 67–85, 1940.
30. Ray, B. S. Ménière's disease; its surgical treatment by division of the acoustic nerve. Am. J. Surg., **75:** 159–170, 1948.
31. Ruskin, S. L. Interrelationship of hydrogen in

concentration, electrolyte content and colloids in permeability of membranes. Arch. Otolaryng., **45**: 398–402, 1947.
32. WALKER, A. E. Ménière's syndrome. J. Omaha Mid-West Clin. Soc., **10**: 46–51, 1949.
33. WALSH, I. E. Symposium. Ménière's disease. Diagnosis. Tr. Am. Acad. Ophth., **60**: 177–181, 1956.
34. WEISS, S. AND LENNOX, W. G. The cerebral circulation. XVII. Cerebral blood flow and the vasomotor response of the minute vessels of the human brain to histamine. Arch. Neurol. & Psychiat., **26**: 737–744, 1931.
35. WILLIAMS, H. L. *Ménière's Disease*. Thomas, Springfield, Ill., 1952.
36. WILLIAMS, H. L. Symposium. Ménière's disease. Etiology. Tr. Am. Acad. Ophth., **60**: 167–171, 1956.

AMYLOIDOSIS IN SENILE AND PRE-SENILE INVOLUTIONAL PROCESSES OF THE CENTRAL NERVOUS SYSTEM

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As early as 1876, Soyka (23) described amyloid deposits of unknown pathogenesis in aged subjects, stating that there was often a predilection for the heart. His publication was not given the attention which it merited because the problem of amyloidosis was invariably related, at the time, to chronic suppurative processes of tuberculosis.

In 1929, however, Lubarsch (12) described a number of cases of amyloidosis which was clearly not a sequela of suppurative processes or tuberculosis. These cases have since been regarded as primary amyloidosis, as distinct from the classical or secondary types. As a rule differ the primary forms from the secondary forms in localization and staining reactions. The German literature therefore sometimes refers to them as para-amyloidosis. Several authors have subsequently pointed out the relationship between senescence and primary amyloidosis, again suggesting the heart as a site of predilection. Hüsselmann (8) found amyloid in the heart in 15 per cent of males and 10 per cent of females over age 70, the smaller blood vessels in other organs also being affected. He believes that this senile cardiovascular amyloidosis is one of the manifestations of primary amyloidosis.

Divry (5) was the first, in 1927, to point out deposits of amyloid in the brain as a sequel of senescence; in his opinion the senile plaques contain a substance which possesses all the characteristics of amyloid.

A few years later Hechst (7) demonstrated that senile plaques have several staining characteristics in common with amyloid. In many plaques, the nucleus is reminiscent of a crystal of radial structure. According to Hechst, the crystalline structure of the plaque nucleus is a characteristic formation of an amyloid deposit. This author also believes that the amyloid is formed in the plaque from breakdown products of the pathological metabolism of nerve cells.

Corten (3) points out that although plaques have several characteristics in common with amyloid (such as metachromasia, the iodine reaction and the positive Congo red test), there are nonetheless differences in reactivity. Staining reactions in plaques are stated to occur later and to be less intensive than those in amyloid. Corten also points out that amyloidosis is not dependent on age, whereas plaques are invariably dependent on the senium, except those seen in Alzheimer's pre-senile atrophy. Amyloid, this author states, can be absorbed, whereas in his opinion absorption of senile plaques has never been demonstrated. He consequently believes that the substance in senile plaques—although resembling amyloid in staining characteristics—is not identical with amyloid

Dias (4) likewise doubts the amyloid nature of senile plaques. Congo red staining —elective for amyloid according to Bennhold—is negative according to Dias, and the metachromasia with aniline colors is never quite so intensive as in the case of genuine amyloid.

Von Braunmühl (1) points out that amyloid staining methods yield no constant results in senile plaques.

Scholz (20) points out that in old age the brain shows vascular changes characterized by deposits in the vascular wall of a homogeneous substance which positively stains with Congo red, is metachromatic

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and birefringent. He believes that this substance is identical with that in senile plaques. He therefore contends that these vascular changes and also senile plaques are manifestations of the same process, to which he refers as "drusige Entartung der Hirnarterien."

Jakob (10), like many other authors, makes mention of the varied staining reactions of senile plaques. In his opinion the differences in results are dependent on the form of the plaques. He contends that the histochemical characteristics associated with certain types of plaque, can afford some information regarding the development of the plaques. All findings tend to show, according to Jakob, that constant morphological and chemical development takes place.

In 1952, Divry (5) presented a survey of the pathological chemistry of senile and presenile processes. In his opinion the nucleus of senile plaques consists of an amyloid spherocrystal with typical birefringence in the shape of a Maltese cross. Apart from the senile plaques, Alzheimer's fibrillar degeneration and "drusige Entartung der Hirnarterien" must also be regarded as a manifestation of amyloidosis. Missmahl and Hartwig (13) also believe that senile plaques should be regarded as manifestations of cerebral amyloidosis.

Pantelakis (15) analyzed the congophile vascular changes in the meninges in advanced age. This congophilia is believed chiefly to affect the arteries. The muscular layer becomes homogeneous; the nuclei largely disappear and the vessel is open and shows a circular transverse section as a sign suggesting loss of elasticity. These vessels stain brown with iodine and metachromatically with cresyl violet. This congophile angiopathy closely resembles Scholz's "drusige Entartung der Hirnarterien"; in both cases there are positive amyloid reactions. However, there are also differences: the congophile angiopathy remains confined to the vascular wall; whereas in the case of "drusige Entartung" the perivascular spaces disappear due to accretion between the adventitia and the limiting vascular membrane, and a congophile deposit sometimes occurs in the adjacent tissues. In addition there may be amyloid deposition on the vascular wall, giving rise to so-called perivascular plaques. Sometimes the amyloid completely detaches itself from the vascular wall, forming freely suspended, spherical congophile bodies to which Scholz refers as nuclear plaques. This congophile angiopathy is therefore regarded by Pantelakis as a pre-stage of "drusige Entartung der Hirnarterien."

Morel and Wildi (14) compared the histochemical characteristics of senile plaques with those of the congophile vascular changes, reaching the conclusion that these characteristics are identical. They believe these characteristics to suggest that protein enters the nervous system via the vessels. Two factors are then involved, *viz.*, a general factor (paraproteinemia) and a local factor in the form of a change in vascular permeability (dyshoria). Senile plaques arise when the dyshoria is confined to the cortical capillaries; congophile angiopathy or "drusige Entartung der Hirnarterien" occurs when the pre-capillaries and the arterioles are also involved in the process.

In 1956, Bülow (2) described a histochemical study of senile plaques, which were found to give a positive PAS reaction. Since the methylene blue extinction test revealed an extinction at pH 4.49–4.17, he concluded that no acid mucopolysaccharides are included in the plaques. This opinion was supported by negative Alcian blue staining. In this author's opinion the plaques contain no glycogen either, as the PAS reaction remains positive following exposure to diastase. The PAS reaction proved to be negative. Bülow also found a markedly positive PAS reaction in the arterial wall. In his opinion the plaques are formed by a substance which arises from the pathological vessels. This substance causes irritation

which, secondarily, gives rise to densification of the ground structure and finally to the plaque proper.

Sperr (24) believes that the congophile cerebral changes must not be regarded as amyloidosis. He found no definite parallelism between intracerebral changes and analogous changes in the other organs. The fact that plaques do not always give positive Congo red reactions also constitutes an argument against their amyloid nature in his opinion. Sperr believes that the congophile substance in the plaques originates from the brain itself, and must be regarded as a precipitate produced by syneresis.

Schiffer (19) also points out that the amyloid reactions in senile plaques are not constant, particularly as to congophilia and iodine affinity. In his opinion, moreover, the metachromasia, positive PAS reaction and Alcian blue staining suggest the presence of acid mucopolysaccharides. As this author understands it, the Alcian blue method reveals a relationship between the plaques and the intercellular tissue in the cortex.

On the basis of her investigation, Wigboldus (28) also formed the conclusion that senile plaques do not always give a positive amyloid reaction. Some cerebral specimens from subjects with senile dementia or with a history of Alzheimer's pre-senile dementia contain numerous plaques with an unmistakable amyloid nucleus, whereas other brain specimens contain many plaques in which no amyloid is found. In her opinion, these differences are related to the morphology of the plaques. She distinguishes four morphological types. The plaques of Type I are generally round, but sometimes show a somewhat irregular outline. They show metachromasia when stained with cresyl violet and stain light brown with Bielschowsky staining. They often show a delicate radial striation, particularly marked at the periphery and sometimes extending just past the circumference of the congophile sphere; these plaques have a diameter of 10 to 20 μ. They are freely suspended in the neural parenchyma. The neurofibrils and axis cylinders are slightly bent apart by these plaques. This Type I corresponds to the nuclear plaque described by Scholz (Figure 1).

Type II includes those plaques in which a nucleus can be distinguished which—morphologically—entirely corresponds to the plaques of Type I. This nucleus is often but not always surrounded by a clear halo which appears to be empty. This halo is outlined by a corona which can be morphologically interpreted as a densification of the ground structure. Glia cells may occur in this corona, and sometimes also in the halo. These plaques are considerably larger than those of Type I, the diameter being 20–60 μ. These plaques unmistakably displace the neural parenchyma. The axis cylinders avoid the plaques in a curved course. No definite neurological reaction is visible around these plaques but the adjacent nerve fibers sometimes show changes such as spindle-shaped swellings or club-shaped runners which may extend into the corona.

The plaques of Type III show fragmentation of the central nucleus. The corona is morphologically equivalent to that of Type II plaques, differing only in that it is often narrower. The disintegrated nucleus is sometimes more or less star-shaped, and the nuclear fragments in other plaques may be arranged in such a manner as vaguely to suggest the spokes of a wheel. In the majority of cases, however, no definite pattern is discernible. The disintegrated nuclei —like the plaques of Type I and the nuclei of plaques of Type II—show metachromasia with cresyl violet and a light brown color upon Bielschowsky staining. The axis cylinders avoid the plaques in a curved course. Fragments of nerve fibers showing club-shaped thickening are sometimes found in the corona. These thickened fiber fragments can show a confusingly marked resemblance to microglia cells. Mild fibrous gliosis is sometimes found around the corona of

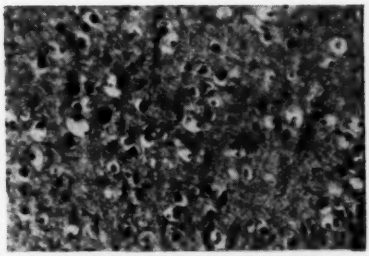

FIG. 1.

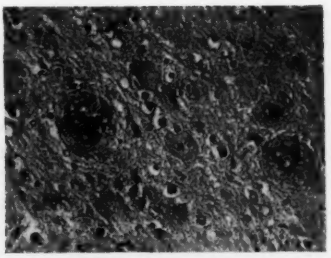

FIG. 2.

FIG. 3.

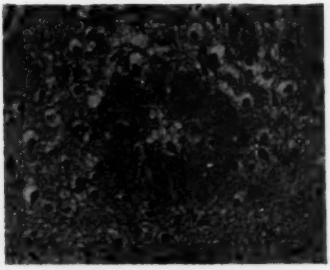

FIG. 4.

FIG. 5.

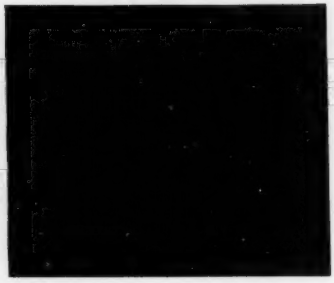

FIG. 6.

FIG. 1. Plaques, Type I.
FIG. 2. Plaques, Type III.
FIG. 3. Plaque, Type IV.
FIG. 4. Plaque, Type IV with optically empty center.
FIG. 5. Plaque nuclei photographed by polarized light.
FIG. 6. Plaque, Type III, photographed by polarized light.

these plaques, particularly in the upper cortical layers. This phenomenon is seldom encountered in the deeper cortical layers. In a varying number of cases, moreover, the plaques show inclusions of glial elements. These glia cells are highly varied in the shape of their nuclei; they are sometimes small and round, with abundant chromatin, and sometimes oval-shaped or even oblong nuclei with a finely granular chromatin distribution. The smallest nuclei are as a rule not surrounded by a definitely recognizable cell body; the larger nuclei are often surrounded by a well-defined cytoplasm, as a rule containing lipofuscin. These cells show the features described by Spielmeyer as "regressive umgewandelte Gliazellen" (Figure 2).

The plaques of Type IV consist of a discoid densification of the ground structure, excellently visible in hematoxylin-eosin specimens (Figure 3) and even more clearly defined in specimens stained with molybdic acid and hematoxylin. An optically empty

center is sometimes seen in these plaques, which may vary in size (Figure 4). These plaques have a diameter varying from 20–60 μ. The typical metachromatic nucleus is entirely lacking, and few cellular elements are visible. One or two small, round, dark glia cell nuclei are sometimes encountered.

The morphology of these plaques allows of definite classification, according to Wigboldus. On the basis of the bipartite structure in the plaques of types II and III moreover, it can be expected that—chemically too—the plaques cannot be considered a unit. This was investigated by a histochemical analysis, always carefully taking into account the morphological type of the plaque examined. The results of this histochemical investigation are presented in Table 1.

The fact that the lipid reactions were in-

TABLE 1

Histochemical Analysis, Results

	Plaques					
	Type I	Type II		Type III		Type IV
		corona	nucleus	corona	nucleus	
Carbohydrate reactions						
Periodic acid-leucofuchsin test (PAS)	+	w+	+	w+	+	w+
PAS reaction after exposure to diastase	+	w+	+	w+	+	w+
PAS reaction after acetylation	−	−	−	−	−	−
PAS reaction after bromation	+	w+	+	w+	+	w+
Alcian blue	+	−	+	−	+	−
Gamma-metachromasia with toluidin blue	−	−	−	−	−	−
Orceine-sulphuric acid reaction	−	−	−	−	−	−
Lipid reactions						
Performic acid Schiff reaction (PFAS)	+	w+	+	w+	+	w+
PFAS reaction after bromation	+	w+	+	w+	+	w+
Sudan black	−	−	−	−	−	−
Sudan III (frozen sections)	−	−	−	−	−	−
Scarlet red (frozen sections)	−	−	−	−	−	−
Reaction of Okamoto *et al.* (for phosphosphingolipids)	−	−	−	−	−	−
Anisotropia (unstained)	−	−	−	−	−	−
Amino-acid and nucleic acid reactions						
Tetrazonium	+	+	+	+	+	+
Bial's neuraminic acid test	+		+			
Gallocyanin-chromaluin	−	−	−	−	−	−
Feulgen reaction	−	−	−	−	−	−
Amyloid reactions						
Metachromasia with methyl violet	+	−	+	−	+	−
Metachromasia with cresyl violet	+	−	+	−	+	−
Congo red	+	−	+	−	+	−
Anisotropia after Congo red staining	+	−	+	−	+	−
Iodine reaction	+	−	+	−	+	−
Iodo-sulphuric acid reaction	±	−	±	−	±	−
King's silver reduction	+	−	+	−	+	−

(The methylene blue extinction test showed that plaques no longer bind methylene blue below pH 4.33.)

variably negative warrants the conclusion that the positive PAS reaction of the plaque nuclei is based on the presence of 1,2-glycol groups. In this case the positive PFAS reaction must not be regarded as a lipid reaction, because it was also positive following bromation. Instead, the positive PFAS is much rather suggestive of proteins (16). The theory that the positive PAS reaction in this case is based on 1,2-glycol groups is further supported by the acetylation test, according to McManus and Cason. The fact that the PAS reaction remains positive following pre-treatment with diastase almost certainly excludes glycogen as an important constituent of the plaques. This leaves acid or neutral polysaccharides or glycolipids, mucoproteins and glycoproteins.

Glycolipids can be excluded on the basis of the negative lipid reactions and the negative orceine-sulfuric acid test. Acid mucopolysaccharides, with toluidin blue, produce a virtually alcohol-resistant gamma-metachromasia in paraffin sections; they bind methylene blue below pH 4 and give a positive reaction with Alcian blue.

Table 1 has shown that the plaque nuclei give no gamma-metachromasia and fail to bind methylene blue under pH 4. A striking fact is, meanwhile, that the Alcian blue reaction is positive. On the basis of the two first mentioned reactions, however, it is improbable that the positive PAS reaction to the plaque nuclei should be based on the presence of acid mucopolysaccharides. It is based, instead, on the presence of either neutral mucopolysaccharides or of mucoproteins or glycoproteins.

The fact that the coupled tetrazonium reaction to plaque nuclei is unmistakably positive shows that they contain a high concentration of proteins; the positive BIAL points in the same direction, indicating as it does the presence of neuraminic acid. Neuraminic acid occurs in two types, *viz.*, as a ganglioside constituent or as an element of proteins. The former possibility can be excluded on the basis of negative lipid reactions. This leaves us with protein material in the plaques, which contains no lipid but does contain a sufficient quantity of diastase-resistant carbohydrate to produce a positive PAS reaction; it gives no gamma-metachromasia with toluidin blue and binds no methylene blue below pH 4. According to Pearse (16), these findings warrant the conclusion that mucoproteins or glycoproteins are involved.

This protein material contains no nucleoproteins, as shown by a negative gallocyanin and a negative Feulgen reaction. The nuclei of the plaques—which can be regarded as conglomerates of mucoproteins or glycoproteins on the basis of this histochemical analysis—invariably produce a positive amyloid reaction. The nuclei stain with Congo red without exception, whereas the plaques of Type IV (which no longer contain a nucleus) fail to stain with Congo red.

Congo red staining is followed by unmistakable anisotropia, the plaque nuclei of Types I and II showing a typical Maltese cross, whereas the disintegrated nuclei of Type III plaques are visible in polarized light as irregular luminescent particles (Figures 5 and 6). The plaques of Type IV proved to contain no birefringent material.

The congophile nuclei showed metachromasia upon methyl violet and cresyl violet staining. King's silver method (highly specific for amyloid according to Pearse) also showed a positive reaction to the plaque nuclei. The classical iodine reaction invariably showed brown coloration of the plaque nuclei. The iodine-sulfuric acid reaction, however, gave varying results. The corona of the plaques of Types II and III gave no positive amyloid reaction, nor did the plaques of Type IV.

The investigation thus demonstrated that the mucoprotein or glycoprotein in the plaque nuclei had indisputable amyloid characteristics. These results correspond to those obtained by investigations into amyloid in the past few years. On the basis of electrophoretic findings, several investigators reached the conclusion that amyloid chiefly consists of globulin. Letterer (11)

concluded that amyloid is composed of protein which resembles the serum globulin. Teilum (26) pointed out that amyloid contains polysaccharide-bearing globulin. According to Richter (17), a β-globulin or one of its derivatives is directly involved in amyloid formation. Wagner (27) emphasized that the composition of amyloid is not constant. He investigated two amyloid cases, finding chiefly α-globulin and a mucopolysaccharide in one, and α- and β-globulin with a mucopolysaccharide in the other. On the basis of these modern investigations amyloid can be assumed to consist of proteins which behave like serum globulins.

Globulins invariably contain fractions in which carbohydrates occur. In 1903, Zanetti (29) found glucosamine, and Rimington, Sörensen and Haagaard also demonstrated mannose and galactose in the prosthetic polysaccharide group. Stary and Yuvanides (25) found hexuronic acid in serum proteins. A detailed analysis of the various carbohydrate components in globulins was carried out by Schultze, Schmidtberger and Haupt (21). They contend that the total concentration in the various fractions varies between three and 40 per cent. Albumin in its pure form is believed to contain almost no carbohydrates; these authors were also able to demonstrate neuraminic acid in the globulin fractions.

All these observations tend to show that the diastase-resistant PAS-positive protein material in the nuclei of senile plaques, which gives typical amyloid reactions, can be regarded as amyloid. Our survey shows, however, that the plaques of Type IV produce no amyloid reactions. Examining brain specimens from aged subjects, we sometimes find many plaques of the first three types, and in other cases a predominance of Type IV plaques. Marked variations can even be encountered within the same specimen. This fact can explain the inconstancy of amyloid reactions, which has been emphasized by various authors. Does this mean that the senile plaques should not be considered a manifestation of amyloidosis? Before this question can be answered, the morphology of the various types must once more be considered.

Type I consists of a spherical amyloid deposit. These free amyloid nuclei are highly similar to the perivascular plaques. It can hardly be denied that a close correlation exists between the perivascular plaques and dyshoric angiopathy. The same substance—amyloid—is found in and around the vascular wall or in freely suspended nuclear plaques. It is consequently highly probable that the nuclear plaques, like the perivascular plaques, are a result of extravasation of amyloid from the vascular wall. Type I is to be regarded also as the first stage. The plaques of Type II have an amyloid nucleus surrounded by a corona which both histologically and histochemically shows the behavior of the intercellular gray substance. Consequently we regard this corona as a reaction of the ground reticulum to extravasation of the amyloid nucleus (plaques of Type I). The morphology of the plaques of Type III can be explained on the basis of fragmentation of the amyloid nucleus. The plaques of Type III would then be a later phase of development of the senile plaque phenomenon. This theory is supported by the fact that the plaques of Type III contain more glia cells than those of Type II. These plaques are sometimes surrounded by a macroglial reaction, and there are often unmistakable signs of degeneration and regeneration in nerve fibers which are bent apart.

This affords histological arguments indicating that Type III plaques are an older phase than those of Type II. Further disintegration of the fragmented amyloid nucleus, and its final absorption, leaves the coronary densification of the ground structure (Figure 4).

After the center of these plaques has been filled from the corona, the features develop which Wigboldus has described as Type IV. This type would thus constitute

the terminal phase of the plaques. It is difficult to establish whether these plaques finally disappear, An argument in favor of the theory that the Type IV plaques constitute the terminal phase of development was found in the fact that numerous plaques of Types III and IV were found in the brains of patients with senile dementia or Alzheimer's pre-senile dementia, in regions showing a marked disturbance in cortical architecture, whereas Type IV plaques were seldom encountered in specimens from aged subjects with a virtually intact cytoarchitecture but showing congophile angiopathy. The investigation showed, moreover, that the various types often occur in groups. In some areas there was a predominance of Types II and III, while adjacent areas chiefly contained Type IV. This indicates that amyloid deposit takes place in waves. This hypothesis regarding the origin and phasic development of senile plaques explains why it is that, although senile plaques should be considered a manifestation of amyloidosis, positive amyloid reactions are not always found in these plaques.

The senile plaques, together with congophile angiopathy, are regarded by us as a manifestation of senile cerebral amyloidosis.

In this connection we agree with Morel and Wildi (14) that proteins originating from the circulation are involved, which are taken up into the vascular wall as a result of changes in permeability (dyshoria). It is from this development that congophile angiopathy arises. As a result of extravasation of amyloid into the cerebral tissue, freely suspended amyloid nuclei are formed which develop into the typical plaques as a result of a reaction of the ground tissue.

On the basis of this hypothesis, there is no fundamental difference between the changes described in senile brains and primary amyloidosis in other organs.

With this hypothesis in mind it must be considered likely that congophile angiopathy is not confined to the nervous system. In order to investigate this point, ten random cases of senile dementia with plaques and congophile angiopathy were examined with a view to the occurrence of congophile vessels in other organs. It was found that congophile angiopathy was not confined to the cerebral vessels but also affected other organs such as the heart, lungs, spleen, kidneys, pancreas and ovaries. Perivascular amyloid deposits were found in some cases. In one case this was very clearly seen in a few periportal spaces in the liver. In other cases, congophile angiopathy was found associated with amyloid deposition in the trabeculae of the spleen and in the perivascular connective tissue in the lungs and the pancreas.

These findings further convinced us that congophile angiopathy and "drusige Entartung" are no specific anomalies of the nervous system. We were supported in our contention that congophile angiopathy and senile plaques are manifestations of a senile amyloidosis which—as stressed by Morel and Wildi—should be probably regarded as a disturbance in the protein metabolism.

SUMMARY

A brief historical review of the literature on amyloid deposition in aged subjects, and on the relationship between amyloidosis and senile plaques, is first presented.

Since Divry first contended, in 1927, that senile plaques are a manifestation of amyloidosis, many investigators have tested senile plaques for the presence of amyloid. The results obtained are widely varied. Many authors who demonstrated amyloid in senile plaques are opposed by as many investigators who failed to find amyloid in the plaques.

The investigation described showed that four morphological types of senile plaques can be distinguished. Histochemical analysis of these plaque types showed that plaques of Types I, II and III contained amyloid, whereas those of Type IV did not.

On the basis of the morphological aspects

and the histochemical analysis of senile plaques the hypothesis is forwarded that senile plaques are a manifestation of senile amyloidosis which starts by deposit of amyloid in the brain tissue, followed by a reaction of the adjacent cerebral parenchym, after which the amyloid is gradually absorbed until only a plaque scar is left in the cerebral tissue, which no longer contains any amyloid. The four plaque types described, therefore, represent four consecutive phases in the plaque-forming process.

The amyloid is likely to be deposited via the vessels, as senile plaques in the brain were almost always associated wth congophile angiopathy of the cerebral vessels. It is pointed out that this amyloidosis of old age is not confined to the brain. Investigations made in a number of cases of amyloidosis of the central nervous system showed that amyloid deposits, and congophile angiopathies, can also be found in various other organs, such as the lungs, heart, kidneys, liver and pancreas.

REFERENCES

1. BRAUNMÜHL, VON A. Neue Gesichtspunkte zum Problem der senilen Plaques. Ztschr. f. d. ges. Neurol. u. Psychiat., **133**: 391–411, 1931.
2. BÜLOW, I. C. Die Anwendung histochemischer Methoden zur Darstellung der Drusen am Gehirn. Arch. f. Psychiat. u. Neurol., **195**: 1–13, 1956.
3. CORTEN, M. N. Ueber die senilen Drusen und ihre Beziehungen zum Hyalin und Amyloid Verhandl. d. deutsch. path. Gesellsch., (Jena) **25**: April 3–5, 1930.
4. DIAS, A. A. Untersuchungen über die senilen Plagues. Ztschr. f. d. ges. Neurol. u. Psychiat., **128**: 23–41, 1930.
5. DIVRY, G. Etude histochemique des plaques séniles. J. belge de neurol. et de psychiat., **9**: 1927. Ref. Zentralbl. f. Neurol., **49**: 619, 1928.
6. DIVRY, G. La pathochimie générale et cellulaire des processus séniles et préséniles. Internat. Congr. Neuro-path., Proc., **1**: 313–345, 1952.
7. HECHST, B. Zur Histochemie und Histogenese der senilen Plaques. Arch. f. Psychiat., **88**: 126–147, 1929.
8. HÜSSELMANN, H. Beitrag zum Amyloidproblem auf Grund von Untersuchungen an menschlichen Herzen. Virchows Arch. f. path. Anat., **327**: 607–628, 1955.
9. JACOB, H. Beiträage zur Histopathologie präseniler Gewebs-veränderungen des Zentralnervensystem. I. Ueber die Struktur-möglichkeiten seniler Drusen und über die fallweise verschiedenen Verläufe "drusige Entartung" der grauen Hirnsubstanz. Ztschr. f. d. ges. Neurol. u. Psychiat., **166**: 313–341, 1939.
10. JACOB, H. Beiträge zur Histopathologie präseniler Gewebsveränderungen des Zentralnervensystems. II. Ueber "verkalkte" senile Drusen (Pseudokalkdrusen). Ztschr. f. d. ges. Neurol u. Psychiat., **172**: 791–796, 1941.
11. LETTERER, E., GEROH, W. AND SCHNEIDER, G. Vergleichende Untersuchungen über den Aminosäurenbestand von Serum-Eiweiss, Lebereiweiss, Amyloid, Hyalin und Kollagen. Virchows Arch. f. path. Anat., **327**: 327–342, 1955.
12. LUBARSCH, O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen. Virchows Arch. f. path. Anat., **271**: 867, 1929.
13. MISSMAHL, H. P. AND HARTWIG, M. Polarisationsoptische Untersuchungen über die Beziehungen zwischen den Drusen und Fibrillenveränderungen im Gehirn bei Alzheimerscher Erkrankung und drusenartigen Ablagerungen amyloider Substanz in anderen Organen. Deutsche Ztschr. f. Nervenh., **171**: 173–180, 1954.
14. MOREL, F. AND WILDI, E. General and cellular pathochemistry of senile and presenile alterations of the brain. Internat. Congr. Neuro-path., Proc., **1**: 347–374, 1952.
15. PANTELAKIS, ST. Un type particulier d'angiopathie sénile du système nerveux central: l'angiopathie congophile. Topographie et fréquences. Monatschr. f. Psychiat. u. Neurol., **128**: 219–256, 1954.
16. PEARSE, A. E. G. *Histochemistry: Theoretical and Applied*. Churchill, London, 1953.
17. RICHTER, G. W. Alterations in serum globulin during the formation and resorption of amyloid in rabbits. J. Exper. Med., **104**: 847–863, 1956.
18. RIMINGTON, C. Biochem. J., **23**: 430, 1929.
19. SCHIFFER, D. Placche senili: contributo allo studio istochimico. Rev. di pat. nerv., **78**: 571–587, 1957. Ref. Zentrabl. f. Neurol. u. Psychiat., **145**: 283, 1958.
20. SCHOLZ, W. Studien zur Pathologie der Hirngefässe. II. Die drusige Entartung der Hirnarterien und-capillaren. Ztschr. f. d. ges. Neurol. u. Psychiat., **162**: 694–715, 1938.
21. SCHULTZE, H. E., SCHMIDTBERGER, R. AND HAUPT, H. Untersuchungen über die gebundenen Kohlehydrate in isolierten Plasmoproteiden. Biochem. Ztschr., **329**: 490–507. 1958.
22. SÖRENSEN, M. AND HAUGAARD, G. Biochem. Ztschr., **260**: 247, 1933.
23. SOYKA, J. Ueber amyloide Degeneration. Prager med. Wchnschr., **1**: 165, 1876.
24. SPERR, W. Zur Frage des gleichzeitigen Vor-

kommens von kongophilen Veränderungen in Gehirn und Körperorganen Seniler. Arch. f. Psychiat. u. Neurol., **196**: 307–315, 1957.

25. Stary, Z. and Yuvanidis, M. Ueber den Hexuronsäuregehalt der Serumproteine. Biochem. Ztschr., **324**: 206–213, 1953.

26. Teilum, G. Periodic-acid-Schiff positive reticulo-endothelial cells producing glycoprotein. Am. J. Path., **32**: 945–960, 1956.

27. Wagner, B. M. Histochemical studies of fibrinoid substances and other abnormal tissue proteins. IV. Protein character of amyloid. A. M. A. Arch. Path., **60**: 221–229, 1955.

28. Wigboldus, J. M. *Over de aard en genese van de plaques seniles.* Dissertation. Amsterdam, 1959.

29. Zanetti, C. U. Gazz. chim. ital., **33**(1): 60, 1903.

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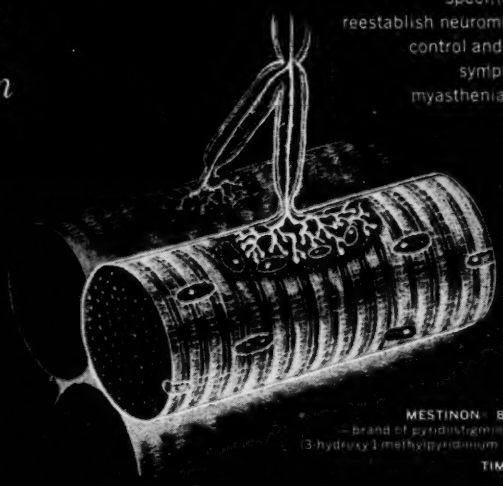

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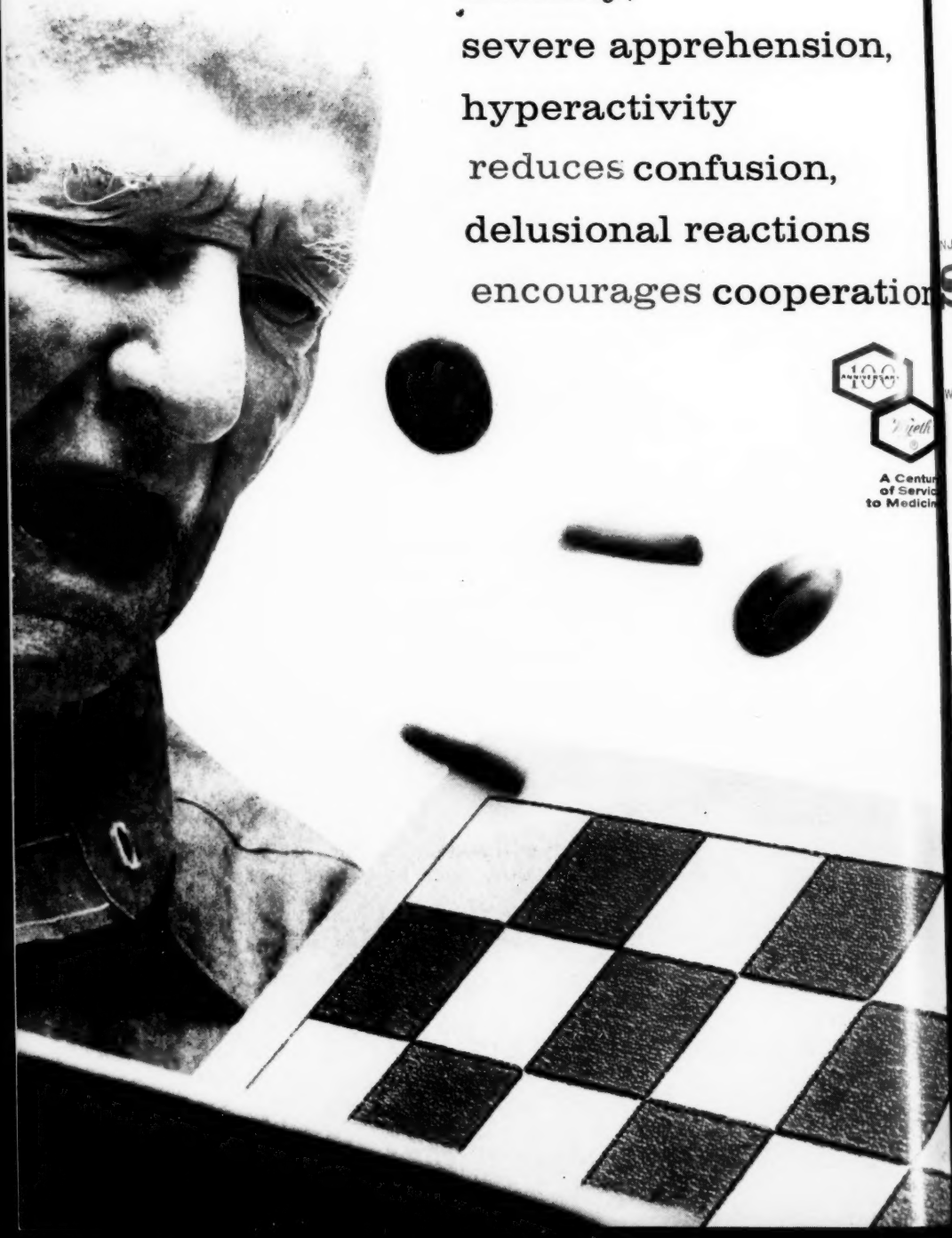

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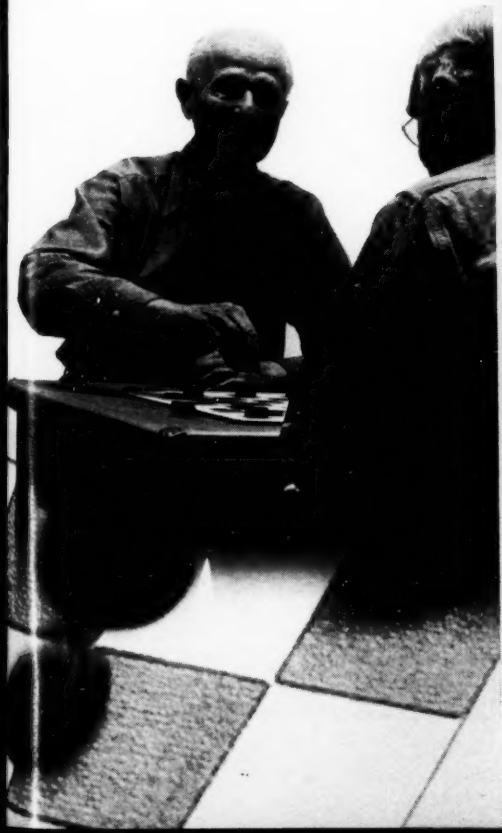

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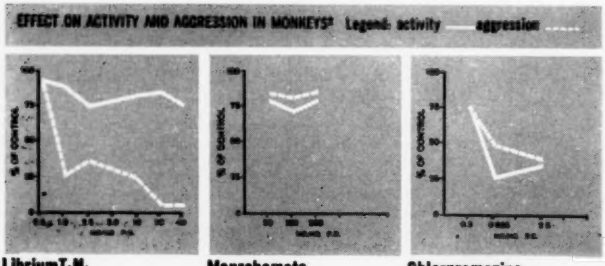

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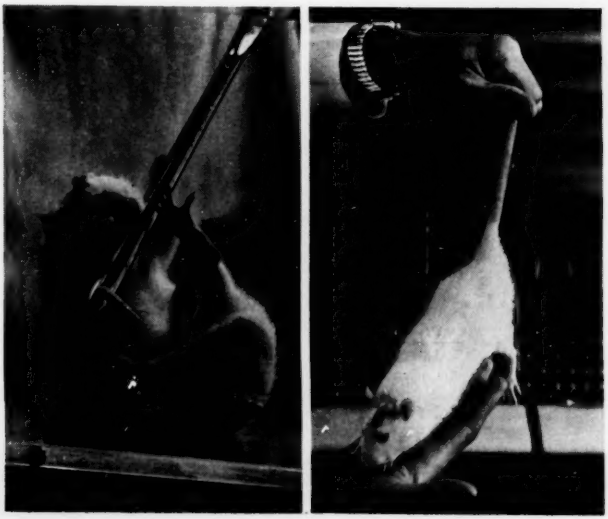
Chlorpromazine
Aggression reduced; **precipitous decrease in activity**

Mice fight each other furiously under mild electric shock administered through bottom of cage. Librium-treated animals fail to show hostility.



Rage reaction (left) is elicited by lifting tail of rat made vicious by destruction of septal area in brain.

Septal rat (right) allows lifting by the tail after treatment with Librium. Rat remains alert.

In the few weeks since its introduction, Librium has met with overwhelming acclaim from all parts of the medical profession. Internists, psychiatrists, cardiologists, gynecologists, dermatologists and many other specialists, as well as tens of thousands of general practitioners, are discovering that the therapeutic applicability of this remarkable new compound transcends that of any tranquilizer or group of tranquilizers.

Here are presented some pertinent pharmacologic and clinical data documenting

NEW 10 mg — and now 5 mg

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THE SUCCESSOR TO THE TRANQUILIZERS

SUCCESSOR IN SCOPE — Librium covers the entire meprobamate range of therapy[6,9] plus a significant portion of the phenothiazine area[9] plus the difficult middle ground between the two.[8] Librium is effective in obsessive-compulsive neuroses which previously have defied drug treatment.[3,4,7,8,17] Librium has a profoundly beneficial effect on depression,[3,6,11] particularly the agitated type.[1,7,9]

SUCCESSOR IN SAFETY — Librium is safer than the most widely prescribed tranquilizing and "equanimity-producing" agents.[6,9,17] Librium lacks the autonomic blocking effects of chlorpromazine and reserpine.[17] Librium is devoid of phenothiazine toxicity;[8,17] free of extrapyramidal complications;[17] and not encumbered by the depressions that often follow reserpine.[8]

SUCCESSOR IN EFFECT — Librium, in addition to relieving anxiety, produces a feeling of well-being, increased drive and a broadening of interest. Librium appears the biggest step yet toward "a pure neuroleptic or 'easing' action totally distinct from a central sedative or hypnotic one."[16]

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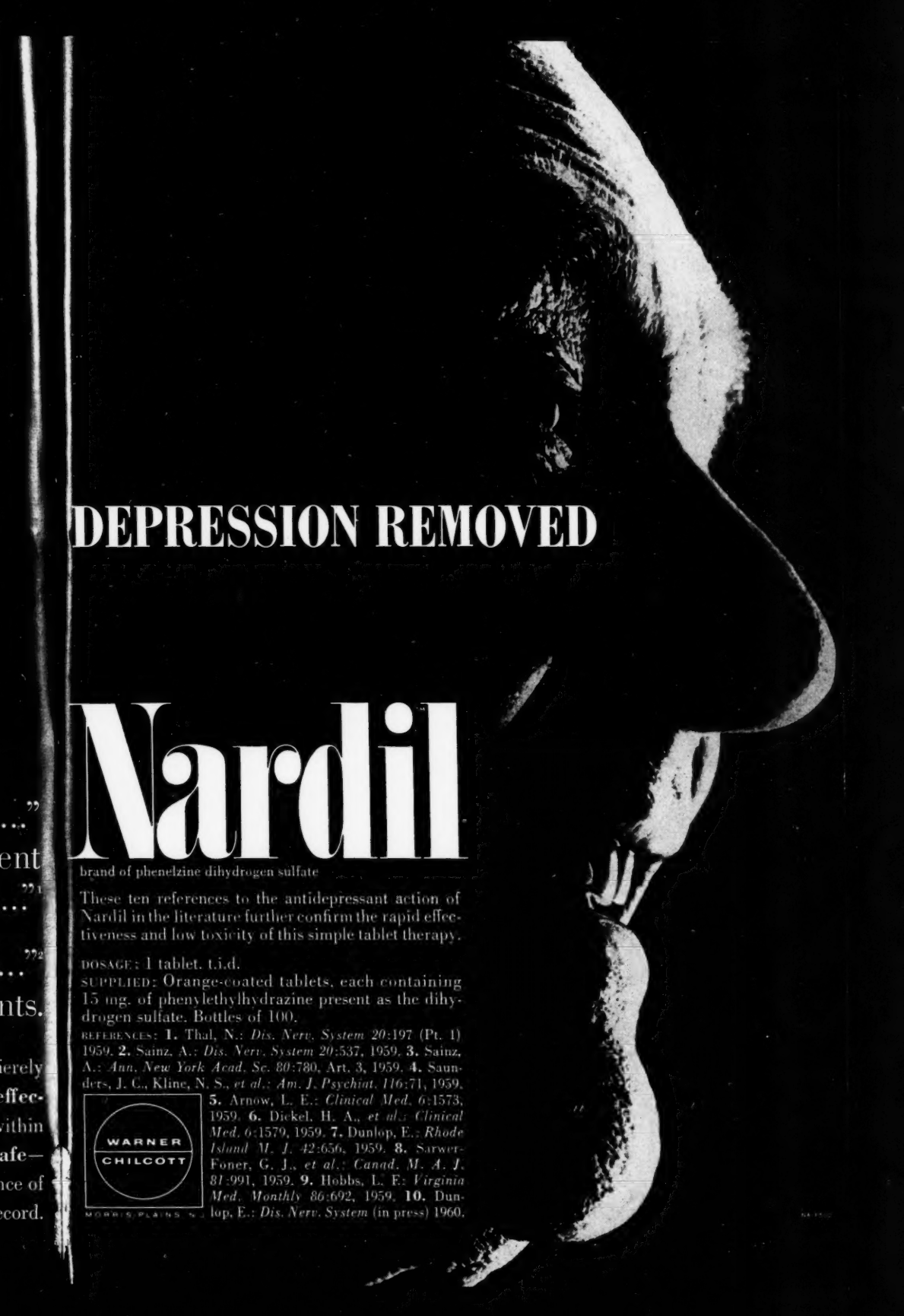
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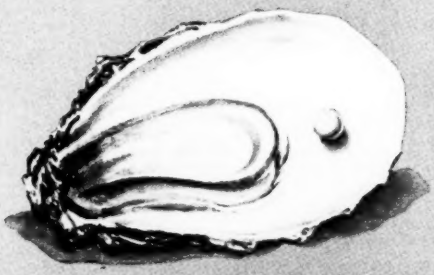

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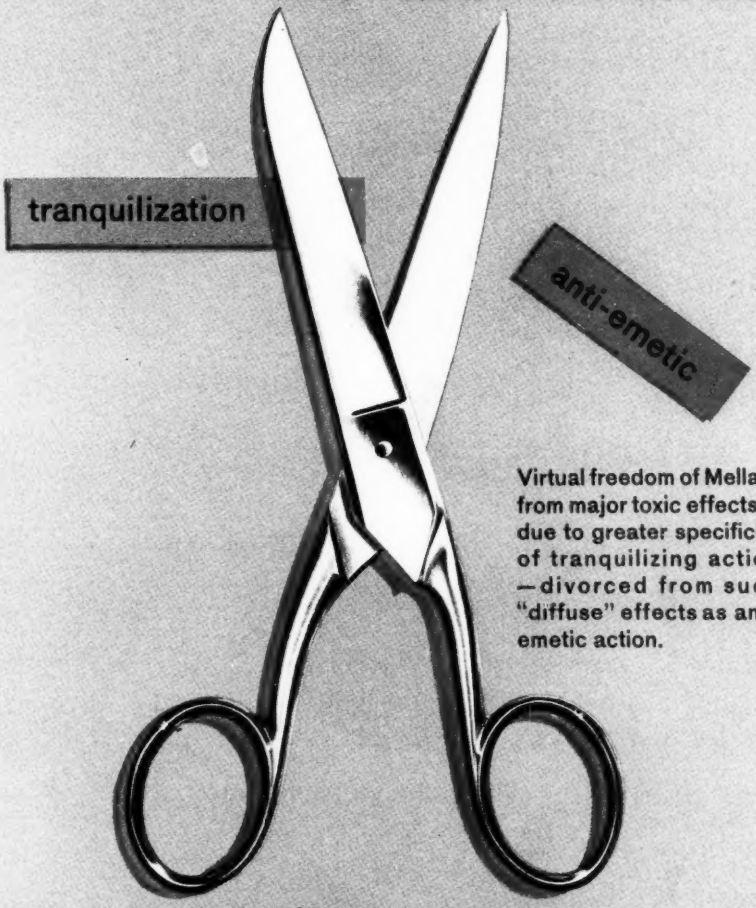

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*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders. J.A.M.A. 170:1283, July 11, 1959.

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Bibliography: **1.** H. F. Darling, W. Kruse, C. F. Hess and M. G. Hoermann, *Dis. Nerv. System*, *20*:269, 1959. **2.** G. C. Griffith, *Clin. Med.*, *6*:1555, 1959. **3.** R. B. Ford, H. E. Branham and J. J. Cleckley, *ibid.*, p. 1559. **4.** H. Azima, H. Durost, D. Arthurs and A. Silver, *Am. J. Psychiat.*, *116*:453, 1959. **5.** L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, *20*:(Suppl.), 26, 1959. **6.** H. F. Darling, *Am. J. Psychiat.*, *116*:355, 1959. **7.** A. L. Scherbel and J. W. Harrison, *Ann. New York Acad. Sc.*, *80*:(Art. 3), 820, 1959. **8.** L. O. Randall and R. E. Bagdon, *ibid.*, p. 626. **9.** G. Zbinden and A. Studer, *ibid.*, p. 873. **10.** O. Resnick, *ibid.*, p. 726. **11.** T. R. Robie, *Dis. Nerv. System*, *20*:182, 1959. **12.** A. Feldstein, H. Hoagland and H. Freeman, *Science*, *130*:500, 1959. **13.** L. O. Randall and R. E. Bagdon, *Dis. Nerv. System*, *19*:539, 1958. **14.** W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. **15.** I. Kimbell and A. Pokorny, paper read at Symposium on Newer Antidepressants and Other Psychotherapeutic Drugs, Galveston, Texas, Nov. 13-14, 1959. **16.** D. Goldman, *ibid.* **17.** J. E. Oltman and S. Friedman, *ibid.* **18.** G. Zbinden, *ibid.* **19.** G. C. Griffith and R. W. Oblath, *ibid.* **20.** H. Freeman, *ibid.* **21.** W. B. Abrams, A. Bernstein, V. D. Mattia, Jr., R. J. Floody and L. O. Randall, Scientific Exhibit, American Medical Association Meeting, Atlantic City, N. J., June 8-12, 1959. **22.** R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. **23.** S. L. Cole, *ibid.* **24.** I. Kimbell, Jr., paper read at Cooperative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959. **25.** L. O. Randall and R. E. Bagdon, Second Marsilid Symposium, Chicago, May 8, 1958. **26.** W. B. Abrams, D. W. Lewis and M. C. Becker, paper read at the International Symposium on Catecholamines in Cardiovascular Pathology, Burlington, Vt., Aug. 23-26, 1959. **27.** H. I. Russek, *Angiology*, to be published.

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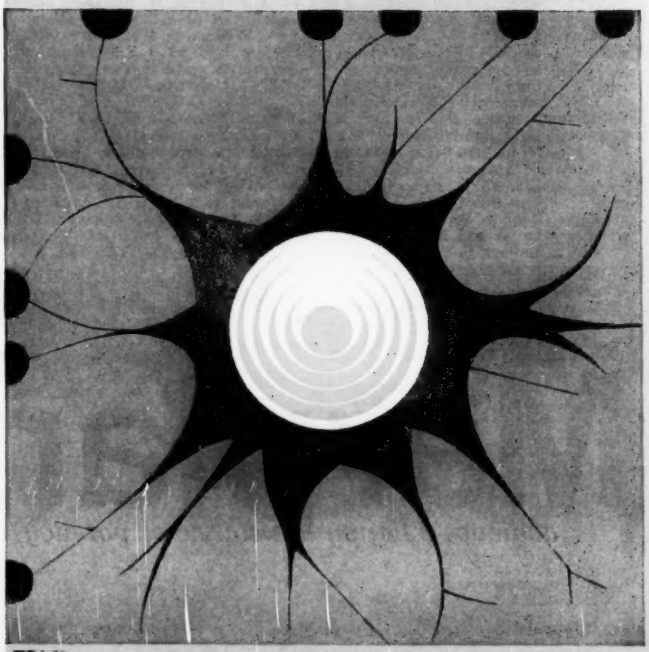

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